Greener Methodology for the Synthesis of α-Diazocarbonyl Compounds and a Novel Approach to Dioxinone Derivatives

Claire O'Brien, B.Sc.

A Thesis Presented for the Degree of

Doctor of Philosophy

to

THE NATIONAL UNIVERSITY OF IRELAND

Department of Chemistry
University College Cork

Supervisor: Dr. Stuart Collins
Head of Department: Prof. Justin Holmes

March 2016

Contents

List of Abbreviations

Ac_2O	Acetic Anhydride
acac	Acetylacetonate
ADMC	2-Azido-1,3-dimethylimidazolinium chloride
aq.	Aqueous
Ar	Aryl
ATR	Attenuated total reflectance
bmim	1-Butyl-3-methylimidazolium
BPR	Back Pressure Regulator
br s	Broad Singlet
BTEAC	Benzyltriethylammonium chloride
Bz	Benzyl
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzyl
CFC	Convection flow coil
cm	Centimetre
conc.	Concentrated
CSTR	Continuously stirred tank reactor
d	Doublet
D	Debye
DAST	Diethylamino sulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM or CH_2Cl_2	Dichloromethane
DEPT	Distortionless enhancement of polarisation transfer
Diazald®	*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine, or Hünig's base
DMA	Dimethyl amine
DMAP	*N*,*N*-Dimethylaminopyridine
DMBP	4,4-Dimethoxybenzophenone
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPMPA	Dipyrolidinomethylaminophosphoric acid triamide
eq. or equiv.	Equivalents
$Er(OTf)_3$	Erbium(III) triflate
ESI	Electron spray ionisation
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl Acetate
EtOH	Ethanol
EWG	Electron withdrawing group
g	Gram
$Gd(OAc)_3$	Gadolinium(III) acetate
$Gd(OTf)_3$	Gadolinium(III) triflate

gem-	Geminal
h	Hour
HCl	Hydrochloric Acid
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMDS	Bis(trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant
k	Rate constant
L	Litres
LAH	Lithium aluminium hydride
m	Multiplet
m.p.	Melting point
MeCN	Acetonitrile
MeOH	Methanol
meq	Milliequivalents
mg	Milligram
MilliQ	Millipore 'ultrapure water'
min	Minute
mL	Millilitre
mmol	Millimoles
mol	Moles
MOM	Methoxymethyl (protecting group)
Ms	Mesyl (methylsulfonyl)
MW	Microwave
NMR	Nuclear magnetic resonance
p-ABSA	4-Acetamidobenzenesulfonyl azide
p-CBSA	4-Carboxybenzenesulfonyl azide
PFA	Perfluoroalkoxy
Ph	Phenyl
ppm	Parts per million
PS-	Polystyrene-supported
PTFE	Polytetrafluoroethylene
q	Quartet
r.t.	Room temperature
R_f	Retention factor
$Rh_2(OAc)_4$	Rhodium(II) acetate
$Rh_2(oct)_4$	Rhodium(II) octanoate
ROM	Ring opening metathesis
s	Singlet
SPE	Solid phase extraction
t	Triplet

T.M. catalyst	Transition metal catalyst
TBS	*t*-Butyldimethylsilyl
Tf	Triflate (trifluoromethylsulfonyl)
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl ether
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl (*p*-toluenesulfonyl)
TsN_3	*p*-Toluenesulfonyl azide
v	Volume
Δ	Heat
µL	Microliters
3-NBBA	3-Nitrobenzenboronic acid

DECLARATION BY CANDIDATE

I declare that this thesis contains my own work and has not been submitted for another degree, either at University College Cork, or elsewhere.

_____

Claire O'Brien

Acknowledgements

I would like to take this opportunity to sincerely thank all the people who helped me throughout my years in UCC. First and foremost, I would like to especially thank Dr. Stuart Collins for the opportunity to work on this project, and for all of his help, encouragement and support throughout my time in the SGC group especially during the preparation of this thesis.

Thanks also to Dr. Dan McCarthy and Dr. Lorraine Bateman for NMR work conducted; Dr. Florence McCarthy and Mick O'Shea for the mass spectroscopy service; Matthias Jauch for help with IT difficulties over the years; Barry O'Mahony for microanalysis and Derry Kearney for his glass blowing service. I would also like to thank the technical staff for their assistance, particularly Tina Kent, Terry Horgan, Dr. Ian O'Connor, Noel Brown, Dr. Michael Cronin, Dr. Nuala Maguire and Dr. Tom O'Mahony. Special thanks to Dr. Alan Ford, Dr. Francis Harrington, Dr. Ben Deadman and Dr. Denis Lynch for always making time to answer my (many) questions. Without financial assistance this thesis would not have been possible, therefore I would like to acknowledge IRCSET and GSK for financial support throughout my PhD studies.

A massive thank you to all the members of the SGC research group past and present; Linda, Elaine, Deirdre, Naomi, Donal, Roisín, Valerié, Patrick, Rose, Laura and especially Chloe. Thank you all for making my experience in 2.14 a truly enjoyable one. Thanks to all the researchers I have had the pleasure of working with over the years, both on the 2nd floor of the Cavanagh and the fourth floor of the Kane – a special mention to the other members of the 2.13 write up area; Kate, Mike, Richard, Jonathan, Davy, Hiren, Pavan, Roisín and Fiona. To Lorraine, whom I have shared my entire college experience with, thank you for all the support, friendship, chats and laughter.

A special thanks to my friends, especially Marie, Jennifer, Lisa and Karen …. Thanks for always being there with a shoulder to lean on, a laugh to be had, a classic boyband tune to be belted out, and a glass of wine or cup of tea as needed! Thanks to Conor for being my favourite penpal – although Skype-pal might be more apt! To Jenny, thank you for your contribution to this thesis in the form of smiles, laughter and encouragement and for always being on the other end of the phone.

A final and sincere thanks to the extended O'Donoghue and O'Brien families, most especially my grandparents and Eleanor for instilling a love of learning in me from an early age. To my brothers Neil and Eoin – Neil, thanks so much for being the epitome of a big brother and always looking out for me, and Eoin, thanks for always being able to make me laugh with your 'hilarious' jokes. To Mam and Dad, words cannot express how grateful I am to you both for all of the support and encouragement you've given me throughout my whole life. This thesis is for the two of you and I hope I made you proud.

_____

Claire O'Brien

Abstract

This thesis outlines a more environmentally benign approach to diazo transfer, and the investigation of the reactivity of α-diazocarbonyl compounds when subjected to transition metal and lanthanide catalysis. Extensive studies were carried out to find the optimum conditions for a greener diazo transfer methodology, and this was also applied to a continuous process for the synthesis of α-diazo-β-ketoesters.

The first chapter includes a literature review of the synthesis and subsequent reactivity of α-diazocarbonyl compounds. An overview of the applications of flow chemistry for the synthesis of hazardous intermediates is also included. The applications of lanthanide catalysts in organic synthesis is also discussed.

The second chapter outlines the extensive studies undertaken to determine the optimum conditions for a greener diazo transfer methodology, including base and solvent studies. Use of water as a viable solvent for diazo transfer was successfully investigated. Diazo transfer to a range of α-diazo-β-ketoesters was achieved using 5 mol% triethylamine or DMAP in water with high conversions. Polystyrene-supported benzenesulfonyl azide as an alternative diazo transfer reagent was also explored, as well as investigations into cheaper generation of this safer reagent. This polymer-supported benzenesulfonyl azide was used with 25 mol% of base in water to achieve successful diazo transfer to a range of α-diazo-β-ketoesters.

The third chapter describes the application of the new methodology developed in Chapter 2 to a continuous processing approach. Various excellent conditions were identified for both batch and flow reactions. A series of α-diazo-β-ketoesters were synthesised with excellent conversions using 25 mol% triethylamine in 90:10 acetone water using flow chemistry. Successful diazo transfer was also achieved using a polymer-supported benzenesulfonyl azide in water under flow conditions.

The fourth chapter discusses the reactivity of α-diazo-β-ketoesters under transition metal and lanthanide catalysis. This chapter describes the synthesis of a range of β-ketoesters *via* transesterification, which were used to synthesise a range of novel α-diazo-β-ketoesters that were used in subsequent decomposition reactions. A novel route to dioxinones *via*

rhodium(II) catalysis is reported. Attempted OH and SH insertion reactions in the presence of various lanthanide(II) catalysts are outlined, leading to some unexpected and interesting rearrangement products.

The experimental details, including spectroscopic and analytical data for all compounds prepared, are reported at the end of each chapter.

Chapter 1

Introduction

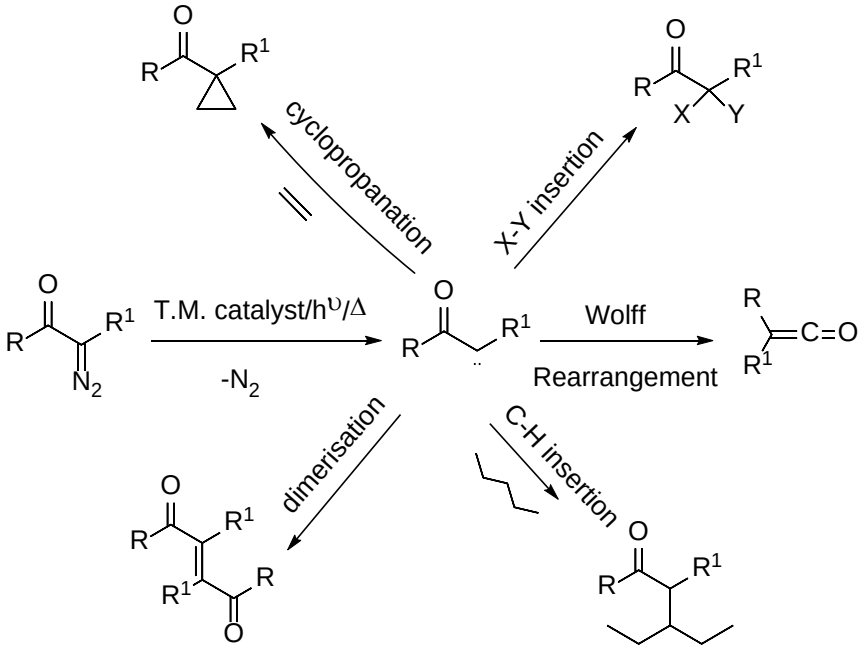
Table of Contents

1.1 Preparation of α-diazocarbonyl compounds

1.1.1 Overview of diazo transfer reactions

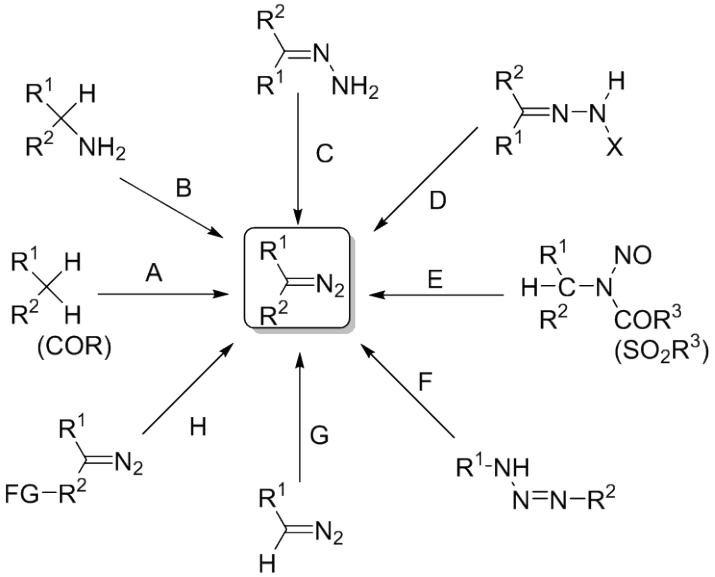
α-Diazocarbonyl compounds are extremely useful in organic synthesis due to their ease of preparation and their diverse reactivity. Decomposition of these compounds under thermolysis, photolysis or transition metal catalysis generates a reactive carbene intermediate. Copper complexes were most commonly used prior to the discovery of the more efficient rhodium(II) carboxylate catalysts in the 1970's.[1,2]

There have been many comprehensive reviews published on the preparation and synthetic uses of α-diazocarbonyl compounds.[3–9] They are a precursor to a series of reactive intermediates which can undergo a range of reactions (**Scheme 1.1**) including Wolff rearrangement, C-H insertion, X-Y insertion, ylide formation, and cyclopropanation. Our understanding of the full potential of the highly reactive diazo functional group is incomplete as the dangers associated with their production limit the frequency of their use in industry. These dangers arise from the reagents employed as diazo transfer reagents, which are often highly sensitive to shock and temperature.[10,11]



Scheme 1.1

There are numerous reported methods for synthesising diazo compounds, which are summarised in recent reviews.[4,5] Several of these routes are highlighted in **Scheme 1.2** below, and include; A) diazo transfer onto an activated methylene group, B) diazotization of α-acceptor-substituted primary aliphatic amines, C) dehydrogenation of hydrazones, D) base treatment of sulfonylhydrazones, E) alkaline cleavage of *N*-alkyl-*N*-nitroso sulfonyl amides, carboxamides, ureas and urethanes, F) triazene fragmentation (rare), G) electrophilic substitution of diazomethyl compounds and H) substituent modification of an existing diazo compound (FG = functional group).

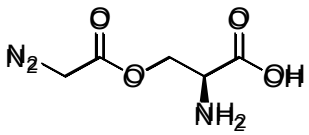


Scheme 1.2

While great progress has been made in the preparation of this class of compounds, they are not yet widely used in the pharmaceutical industry. The diazo functional group is present in many natural products, therefore development of a route to these compunds which has an increased safety profile would have a market within pharmaceutical development. Moody and Nawrat have compiled a comprehensive review of natural products that contain a diazo group.[12] A selection of these are outlined here.

Azaserine **1** is the most widely studied naturally occuring diazo compound. It was reported in 1954, after being isolated from *Streptomyces fragilis* as part of a screening program for new antitumour and antiobiotic agents.[13–15] **1** has been shown to be active against leukemia,

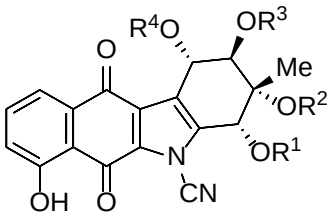
however, following clinical trials it was found to be less active than other agents. It is used as a glutamine antagonist.



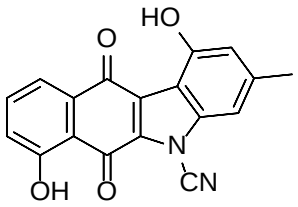
1

Figure 1.1

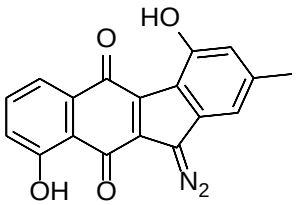
The kinamycins **2** and **3**, and related prekinamycins **4** and **5** shown in **Figure 1.2** are powerful antitumour antibioitcs. The kinamycins were isolated from *Streptomyces murayamaenis* in 1970 and a number of total syntheses have been published.[16–18]



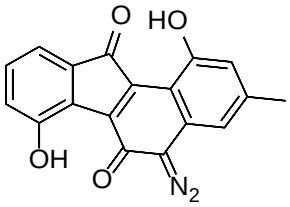
2



3



4

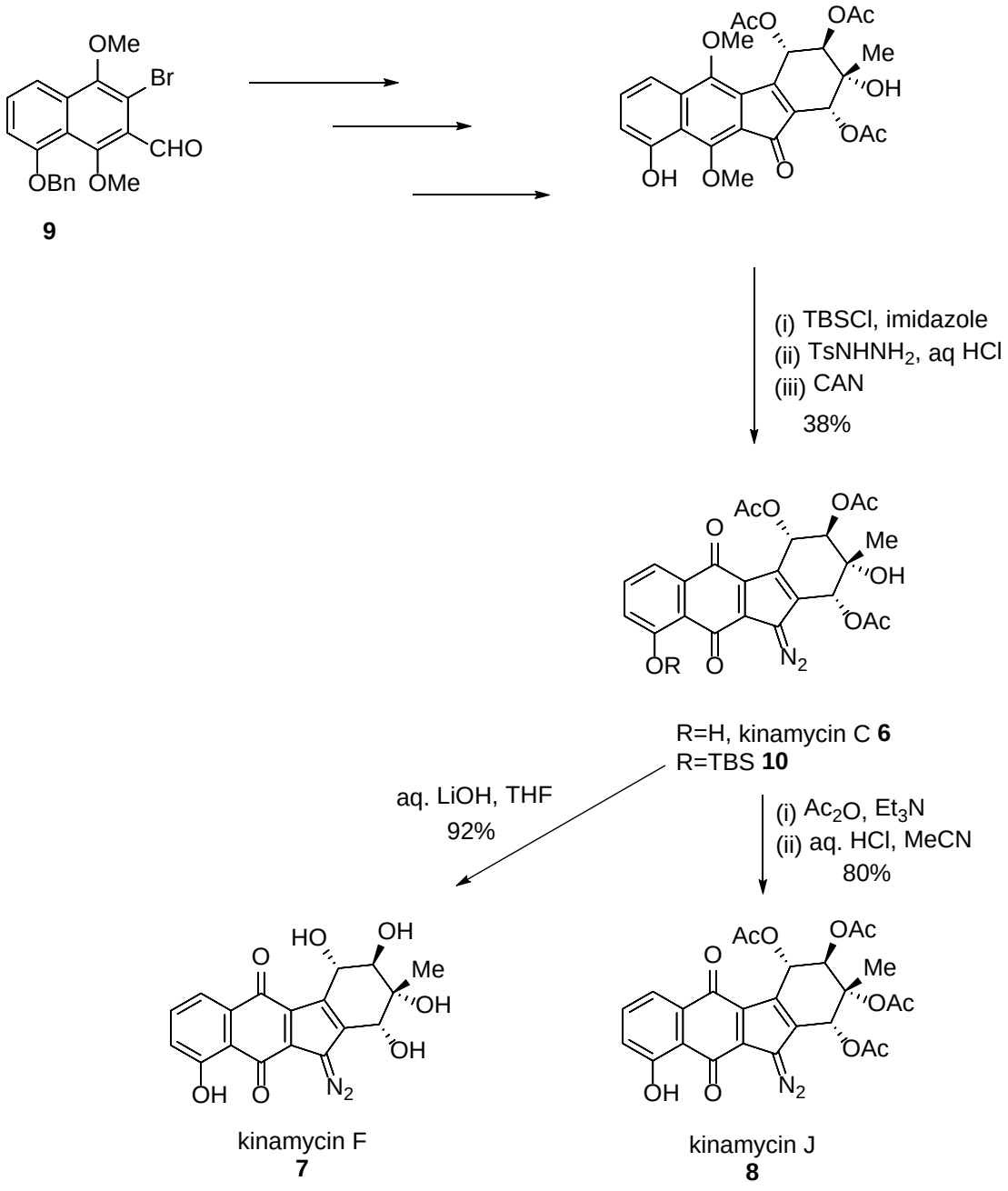


5

Figure 1.2

The total synthesis of kinamycins C **6**, F **7** and J **8** were reported by Nicolaou and co-workers.[18] Starting from **9** kinamycin C is accessible in four synthetic steps. The diazo functionality is introduced in the last step by formation of the tosyl hydrazine, and subsequent oxidation to the diazo group by ceric ammonium nitrate (CAN). When formed as the TBS-

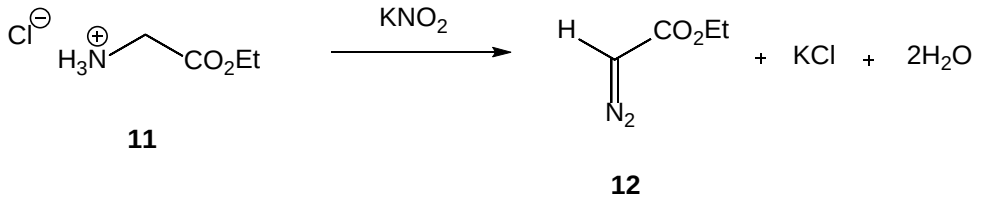
ether **10**, kinamycins F and J can be accessed in just one additional synthetic step as illustrated below in **Scheme 1.3**.



Scheme 1.3

1.1.2 A brief history of diazo chemistry

The first reported synthesis of an α-diazocarbonyl compound was in 1883, when Curtius synthesised ethyl diazoacetate **12** from glycine ethyl ester hydrochloride **11** (**Scheme 1.4**).[19,20] Since this early work, significant advances have been made in the field of diazo chemistry, many of which will be outlined in the following sections.

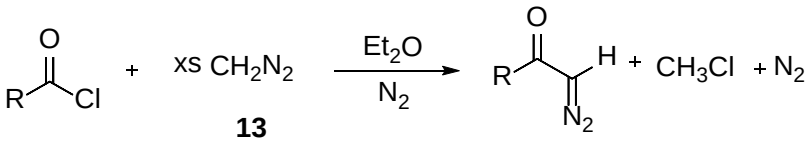


11 **12**

Scheme 1.4

1.1.2.1 Arndt-Eistert synthesis

Diazocarbonyl compounds with simple alkyl side chains became available through the work of Arndt and Eistert in 1927,[21–24] and Bradley and Robinson in 1928.[25] The authors reported the synthesis of diazoketones by addition of an acyl chloride to ethereal diazomethane **13** (at least 1-2 equiv excess) at or below 0 °C, illustrated below in **Scheme 1.5**.



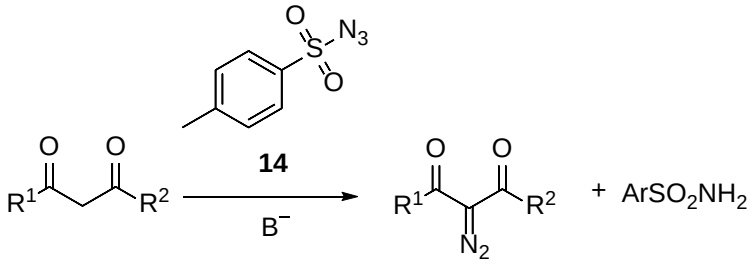
13

Scheme 1.5

It was previously believed that this reaction was only capable of producing chloromethyl ketone. However the authors determined that by using an excess of diazomethane **13**, it was possible to trap the hydrogen chloride produced in the course of the reaction, therefore preventing its reaction with diazoketone.

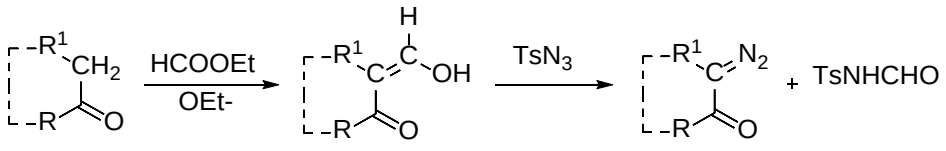
1.1.2.2 Regitz diazo transfer method

The most common method for the transfer of a diazo group is the procedure described by Regitz.[26,27] This method involves deprotonation of the substrate by a base of sufficient strength, followed by transfer of the N_2 group by a donor, invariably a sulfonyl azide (**Scheme 1.6**). Of the sulfonyl azides, *p*-toluenesulfonyl azide (tosyl azide) **14** is still the most widely used. Prior activation of the substrate may be necessary to achieve good conversion to the desired products.[28] Therefore substrates can be divided into two categories – those with sufficiently activated methylene protons such as β-keto esters, malonic esters and β-diketones will readily undergo diazo transfer.



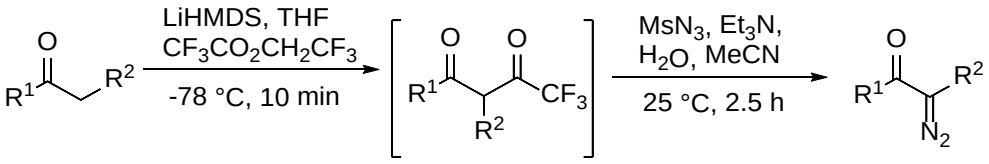
Scheme 1.6

For the second category of substrates, where the methylene group is activated by only a single carbonyl group, the standard Regitz methodology is less successful. In these cases it is often necessary to first activate the substrate by a method called deformylating diazo transfer.[26,27] This is carried out by Claisen condensation of the ketone with ethyl formate as shown in **Scheme 1.7**. This introduces an additional electron withdrawing group in the form of the strongly activating formyl group, which is subsequently released as the sulfonyl amide in the course of the diazo transfer reaction. This allows the successful synthesis of most types of acyclic and cyclic α-diazoketones.[29,30]



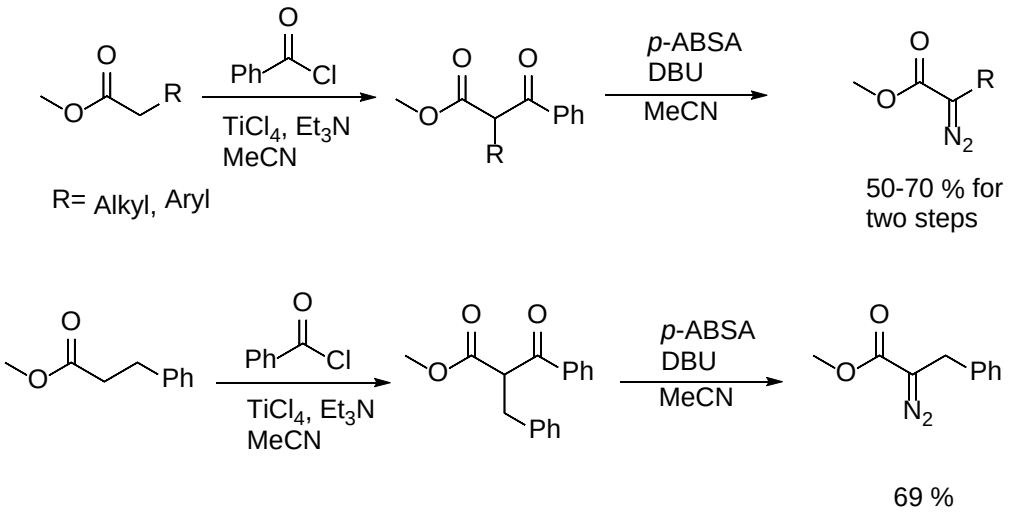
Scheme 1.7

Improvements on this method have been described by Danheiser *et al*.[31,32] Danheiser found that the harsh conditions required for the Claisen condensation could be replaced by use of trifluoroacetylation of kinetically generated lithium enolates. This improved the efficiency of the diazo transfer reactions, and is referred to as a trifluoroacetylation/detrifluoroacetylation diazo transfer (**Scheme 1.8**).



Scheme 1.8

Another modification of Regitz's method was reported by Taber *et al*.[33] This method involves the $TiCl_4$-mediated reaction of an ester with benzoyl chloride resulting in high yields of the α-benzoylated ester, which can then undergo efficient diazo transfer. This method allows the easy preparation of gram quantities of α-diazo esters, and is more accessible than the Danheiser acylation method, which requires the use of an expensive strong base and cryogenic conditions. This method is known as benzoylation/debenzoylation diazo transfer, and is illustrated below in **Scheme 1.9**.

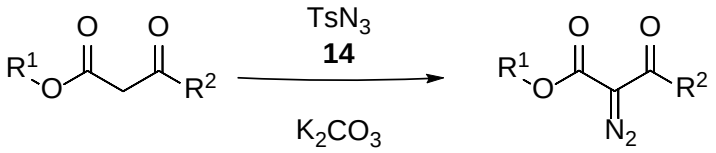


Scheme 1.9

1.1.2.3 Other modifications to the Regitz method

There are two major concerns with the standard Regitz methodology that prevent it being used on an industrial scale. If these issues could be overcome, the potential of the diazo functionality could be unlocked and used to access a diverse range of chemistry and functionality for pharmaceutical processes. The first is the inherent instability of the diazo transfer reagents. Issues with their thermal and shock sensitivity must be addressed in order to use this method on an industrial scale, and this will be discussed in **Section 1.2.2**. The second issue is the difficulty associated with removing the sulfonyl amide by-product to give the pure diazo product. While this has been addressed with some of the newer diazo transfer reagents,[34–36] other approaches have also been developed.

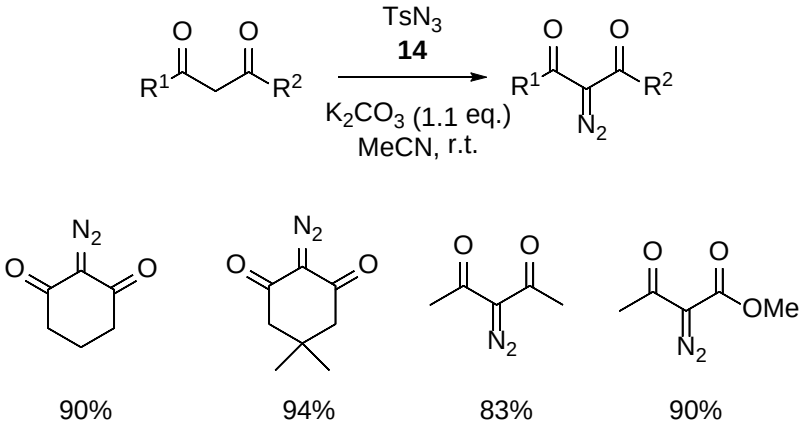
Koskinen *et al*. reported diazo transfer under mildly basic conditions, using potassium carbonate in acetonitrile.[37] This method can be used to access a range of diazo-malonates and α-diazo-β-ketoesters, using equimolar quantities of potassium carbonate as base, at room temperature. An added bonus of this method is that addition of a non-polar organic co-solvent precipitates the sulfonyl amide by-product, and so purification is by filtration only.



R^1=R^2= Me, 96%
R^1=Bu^t, R^2=OEt, 86%

Scheme 1.10

Another successful method for purifying diazo compounds from the Regitz methodology without diminishing the yield was described by Presset and co-workers.[38] A range of diazo transfer reagents and purification techniques were tested, and *p*-tosyl azide **14** followed by purification on silica gel and/or alumina gave the highest yields and the most reproducible results. Use of both silica gel and alumina in the purification process allowed complete removal of the sulfonyl amide by-product (**Scheme 1.11**).



Scheme 1.11

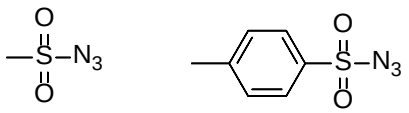
1.2 Diazo transfer reagents

1.2.1 Comparison of classical and modern diazo transfer reagents

As no single reagent is suitable for all diazo transfer reactions, a number of factors must be considered when choosing an appropriate reagent. The reagent of choice will satisfy the following criteria:

- Have readily available starting materials
- These starting materials should be inexpensive
- The azide would preferably have a low explosive potential, and
- The resulting sulfonyl amide should be easily separable from the diazo product.

There are numerous reviews in the literature[7,26,27,39] on the wide range of diazo transfer reagents available[40–46] as well as their individual properties including hazards, stability and safety.[10,45] A review has been carried out by Bollinger *et al.*,[10] which found that methanesulfonyl azide (mesyl azide) **15** was the most dangerous of the reagents reviewed, with the highest impact sensitivity and the largest heat of decomposition. A close second to mesyl azide in impact sensitivity is *p*-toluenesulfonyl azide (tosyl azide) **14**, and although the authors strongly advise against the use of mesyl azide, they acknowledge tosyl azide as being widely used (**Figure 1.3**).

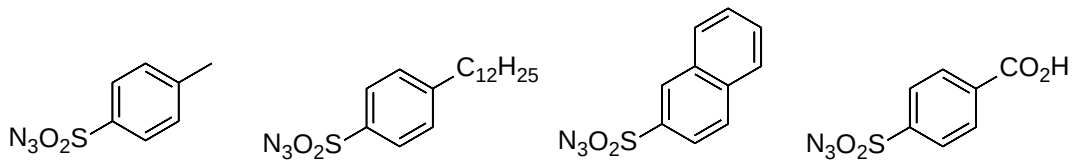


15 **14**

Figure 1.3

Bollinger *et al*. reported the *p*-dodecylbenzenesulfonyl azides **16** as having the smallest specific heat of decomposition, as well as second highest initiation temperature of the ten azides tested. *p*-Dodecylbenzenesulfonyl azide also displayed no impact sensitivity at the highest test levels making it the safest reagent reported. As can be seen in **Table 1.1**, the corresponding sulfonyl amide is a liquid, and therefore has the extra advantage of ease of separation from any crystalline diazo products. The relatively good safety profile of reagent **16** is reflected by their use for large scale diazo transfer reactions for over 9 years at Merck without incident.[45] The reagent **16** is stable for prolonged periods of storage without noticeable deterioration in the freezer (-20 °C).

Table 1.1 ***Properties of some common diazo transfer reagents***



14 **16** **17** **18**

Sulfonylazide	m.p. (ºC)	Initiation Temp. (ºC)	Rate of Decomp.[a]	Impact Sensitivity Kg cm^{-1}	Sulfonylamide m.p. (ºC)
14	19-20	~120	1.00	50	135.7-137
16	Liquid	~151	0.36	-ve to 150	Liquid
17	41-43	~146	0.96	300	218.5
18	184-186	~163	2.29	300	295-296

Table 1.1 shows that naphthalene-2-sulfonyl azide **17** has low impact sensitivity and a highly crystalline, poorly soluble by-product, which allows easy separation from liquid diazo products. Another diazo transfer regent found to have an improved safety profile over tosyl azide **14** is *p*-carboxybenzenesulfonyl azide **18**. This reagent has the advantage of being water soluble, but the disadvantage of requiring an excess of base for activation, making it unsuitable for base sensitive substrates. The trimethylamine salt of this acid is soluble in acetonitrile, while its by-product is insoluble – which can be used to facilitate purification of the diazo product.

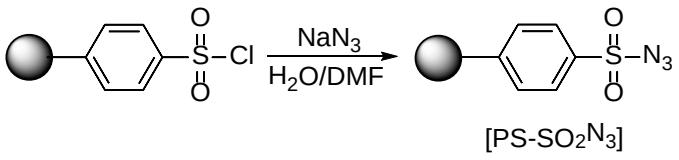
1.2.2 Progress towards safer diazo transfer reactions/reagents

Various diazo transfer reagents have been developed in an attempt to demonstrate to the pharmaceutical industry that diazo compounds could be part of their chemical armoury if their synthesis could be scaled up safely. The risks associated with preparing and using traditional diazo transfer reagents have been well reported in the literature.[10,45] Consequently, interest in the development of safer alternatives has seen the development of a range of diazo transfer reagents with improved safety profiles, greater ease of handling, and easier isolation of the diazo-product. The following section shows a selection of the recent breakthroughs in safer alternatives to the traditional transfer reagents.

Polystyrene-supported benzenesulfonyl azide

Green and co-workers[36] developed a polymer-supported benzenesulfonyl azide **19** which has the following benefits compared to the standard unmodified reagent:

- Thermally stable
- Is not friction sensitive
- Easy preparation and handling
- Improved safety profile
- Ease of purification of the diazocarbonyl product – the resin containing sulfonyl amide by-product can be removed by filtration, with no need for an aqueous work-up.



20 **19**

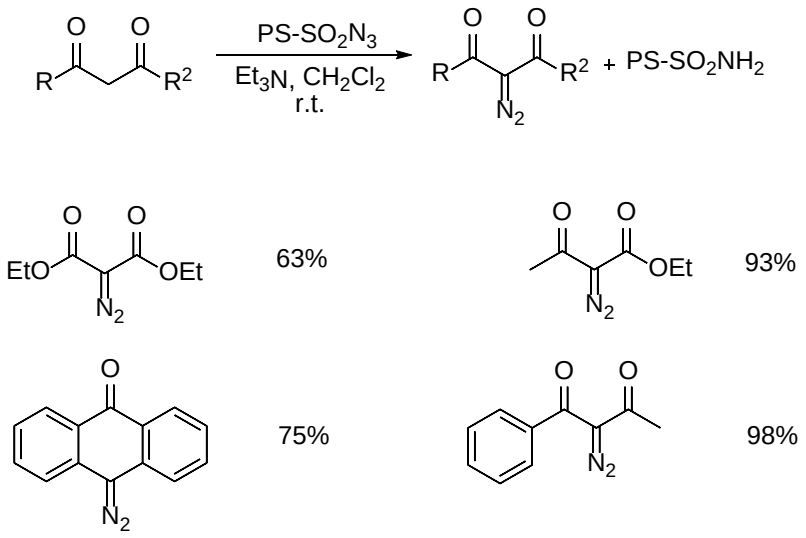
Scheme 1.12

The polymer-supported benzenesulfonyl azide resin **19** is prepared in one step from commercially available polymer-supported benzenesulfonyl chloride **20** by reaction with sodium azide at room temperature, as illustrated above in **Scheme 1.12**.

The standard tosyl azide **14** needs to be stored in the freezer in an isolated container and then carefully warmed to room temperature before use. Extreme caution must be taken in its handling and care must be taken when pipetting the liquid that it doesn't come into contact with any sharp edges. In contrast the polymer-supported benzenesulfonyl azide **19** can be stored on the bench and has much easier handling as it can be easily weighed out in the solid form.

Green and co-workers achieved successful diazo transfer to a range of substrates including β-ketoesters and diketones in good to excellent yields (**Scheme 1.13**). Once the reaction was complete, the polymer-supported benzenesulfonyl amide was removed by filtration to give pure α-diazocarbonyl product on removal of solvent. This is in direct contrast to standard tosyl azide which requires an aqueous work-up to remove *p*-toluenesulfonyl amide by-product **21**, and sometimes column chromatography to remove any unreacted tosyl azide and residual sulfonyl amide.

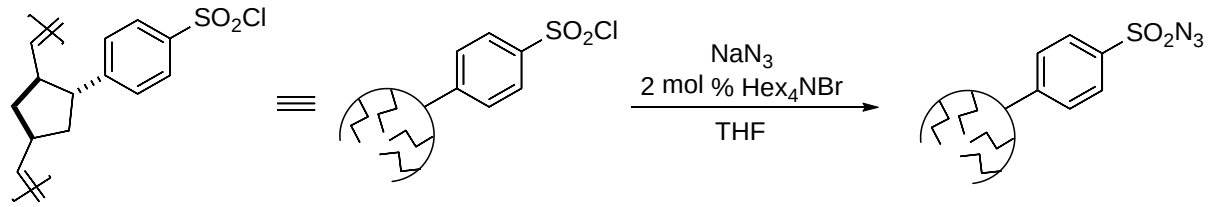
Green used solution-phase reagent 4-carboxybenzenesulfonyl azide (*p*-CBSA)[30] **18** in direct comparison reactions, and found that yields in both cases were similar, although *p*-CBSA often required longer reaction times.



Scheme 1.13

Oligomeric benzenesulfonyl azide

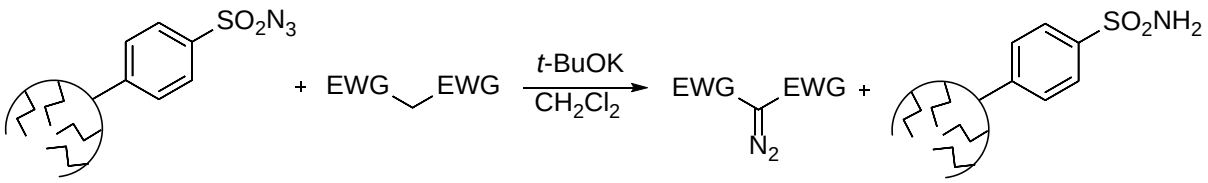
Hanson *et al*. reported construction of a high loading, soluble oligomeric benzenesulfonyl azide **23** using cheap, readily available starting materials *via* ring-opening metathesis (ROM) polymerization.[35] High loading on the oligomer is ensured by functionalising the monomer, before forming the active polymer *via* (ROM) polymerization. In this case, monomeric benzenesulfonyl chloride was formed, polymerized and then treated with sodium azide in the presence of a phase transfer catalyst, Hex_4NBr, to give oligomeric benzenesulfonyl azide, as shown in **Scheme 1.14**.



22 **23**

Scheme 1.14

A major benefit of this reagent is that it is soluble in organic solvents such as DCM, THF and DMF, while its sulfonyl amide by-product is not. Therefore, filtration through a silica gel solid-phase extraction (SPE) cartridge yields pure diazo product.



23

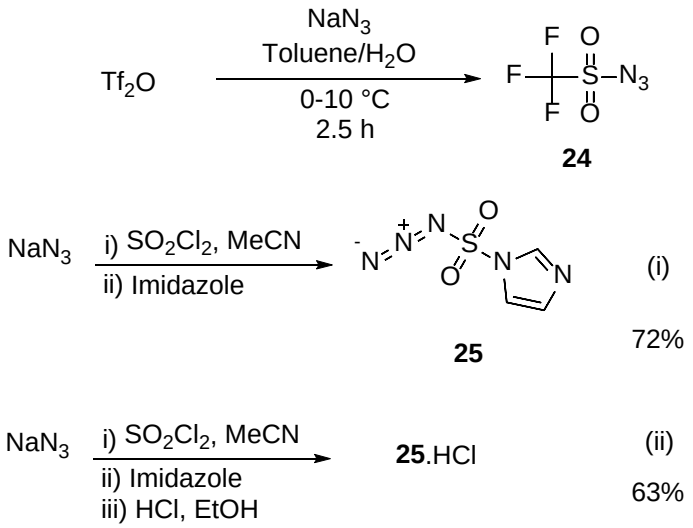
Scheme 1.15

The authors reported successful diazo transfer to a range of esters, ketones and phosphonate esters, as shown above in **Scheme 1.15.** The diazo compounds were formed in good to excellent yields (74-97%) and excellent purities following purification by filtration of the crude mixture.

Imidazole-1-sulfonyl azide hydrochloride

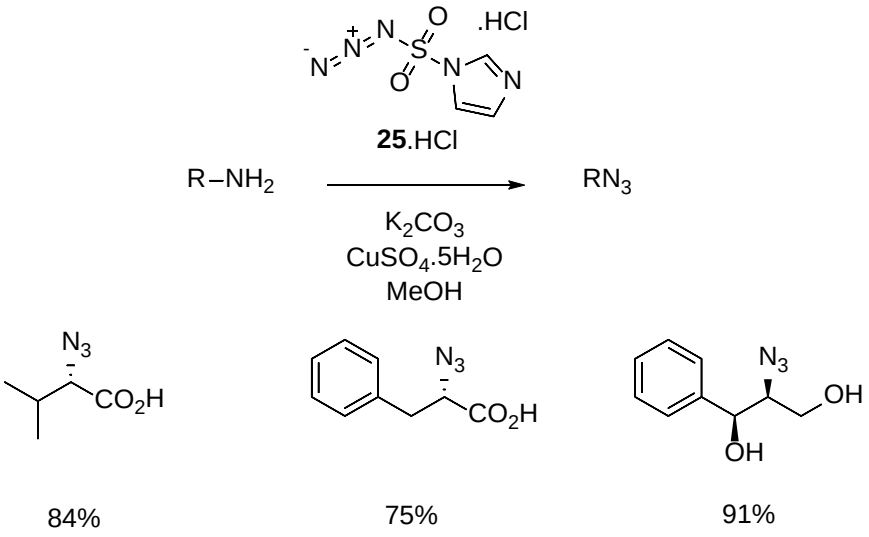
Goddard-Borger *et al*. reported imidazole-1-sulfonyl azide hydrochloride **25**.HCl as a crystalline, shelf-stable, and easily prepared alternative to trifyl azide (TfN_3) **24** in diazo transfer reactions.[47] Trifyl azide **24** has a poor shelf and must therefore be prepared in solution before use.[48] The expense of trifluoromethanesulfonic anhydride, used in the preparation of **24**, prevents its use on a large scale. In addition to this, inconsistent yields in the synthesis of trifyl azide mean that the solution must either be standardised or used in a liberal excess.

Due to the drawbacks associated with trifyl azide, the authors endeavoured to generate a diazo transfer reagent that was equally efficient but without the associated problems. This required finding an electron-withdrawing group capable of replacing the trifluoromethanesulfonyl moiety. Imidazylates exhibit similar reactivity while having the advantage of being relatively inexpensive to prepare, while enjoying a longer shelf life.



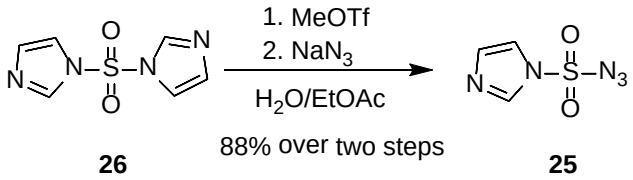
Scheme 1.16

One of the main aims had been to generate a convenient crystalline diazo transfer reagent and so the hydrochloride salt of **25** was formed as a colourless crystalline solid (**Scheme 1.16)**. This salt was successfully used to prepare a range of diazo compounds, as well as being used to convert a range of amines into the corresponding azides in excellent yields, as seen in **Scheme 1.17**.



Scheme 1.17

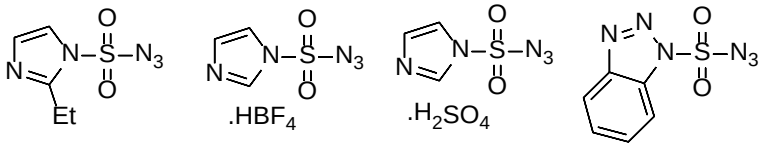
Ye and co-workers[49] later reported a safer synthesis of **25** in a bid to eliminate the explosion hazard associated with hydrazoic acid, which can form as a by-product in the Goddard-Borger synthesis from reaction of hydrochloride with sodium azide. This new synthesis, shown in **Scheme 1.18**, involves reaction of sulfuryl diimidazole **26** with methyl triflate, with subsequent addition of sodium azide in water-ethyl acetate (95:5).



26 **25**

Scheme 1.18

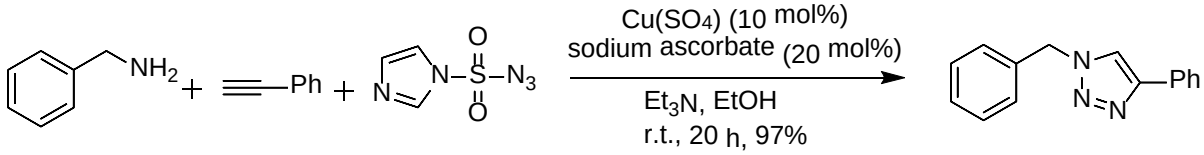
This synthesis can be scaled up considerably and is the first report of a safe preparation of a sulfonyl azide derivative at >100g scale. Some structural modifications of **25** such as **27**-**30**, have been investigated and reported to have improved chemical properties or an increased safety threshold (**Figure 1.4**).[49–52]



27 **28** **29** **30**

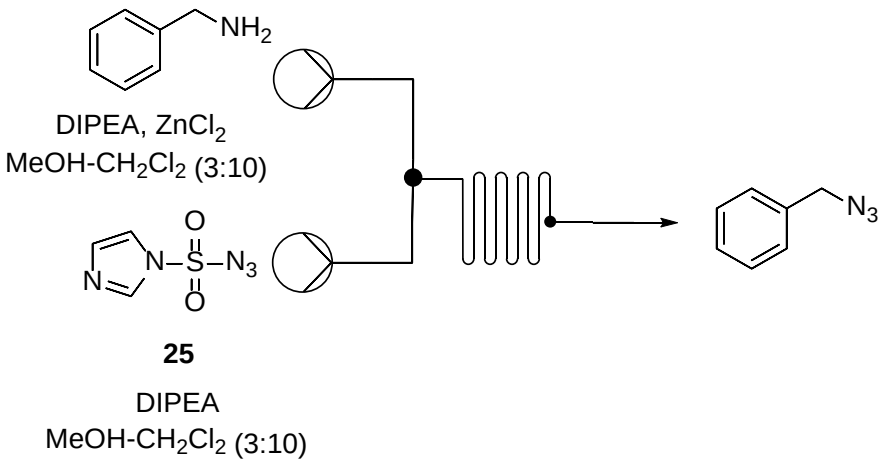
Figure 1.4

Since imidazole-1-sulfonyl azide was first reported, it has been widely used: Smith *et al*. used **25** to establish a one pot procedure for the synthesis of 1,2,3-triazoles from primary amines and terminal acetylenes *via* copper-catalysed click chemistry (**Scheme 1.19**).[53]



Scheme 1.19

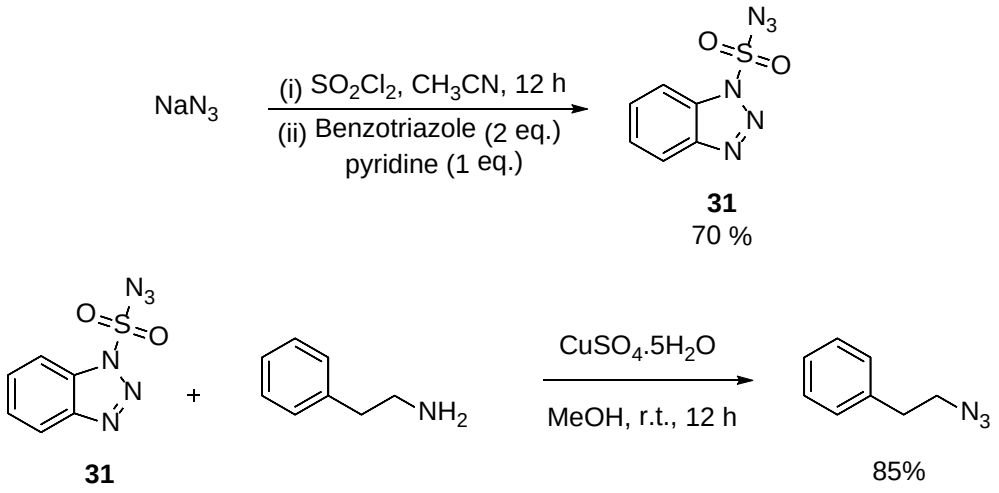
Delville and co-workers used **25** for the optimization of a continuous flow system for the preparation of organic azides, as shown in **Scheme 1.20**.[54] Continuous flow microreactors are ideally suited to potentially explosive azide synthesis due to the intrinsically small volumes and highly controlled reaction conditions.



Scheme 1.20

Benzotriazol-1-yl-sulfonyl azide

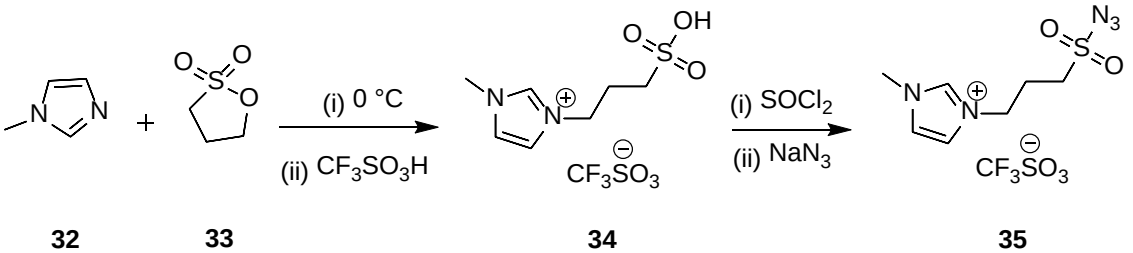
The preparation of benzotriazol-1-yl-sulfonyl azide **31** was reported by Katritzky and co-workers.[50] They reported a new crystalline, stable and easily available diazo transfer reagent, which was intended for use forming azido-protected peptides, esters, ketones and thioesters. Chlorosulfonyl azide was prepared *in situ* from sodium azide and sulfuryl chloride, then reacted with benzotriazole and pyridine in acetonitrile to access benzotriazol-1-yl-sulfonyl azide **31** in good yields, as shown in **Scheme 1.21**. The reagent remained stable six weeks after its preparation and has high solubility in both organic and partially aqueous solvents. Benzotriazol-1-yl-sulfonyl azide **31** was successfully used by the authors to synthesise a wide range of azides and diazo compounds, an example of which is shown in **Scheme 1.21**.



Scheme 1.21

Ionic liquid-supported sulfonyl azide

A unique diazo transfer reagent was reported by Kumar *et al*. in the form of an ionic liquid-supported sulfonyl azide.[34] Ramachary and co-workers had achieved ionic liquid promoted diazo transfer reactions using traditional diazo transfer reagents.[55] Kumar extended this work and created an ionic liquid that acted as both reagent and solvent. The reagent **35** was successfully synthesised by reaction of 1-methylimidazole **32** with 1,3-propanesultone **33**, followed by reaction with trifluoromethanesulfonic acid (TfOH). The resulting ionic liquid **34** was then further functionalised by reaction with thionyl chloride, followed by sodium azide to give the ionic liquid-supported sulfonyl azide **35**, as seen below in **Scheme 1.22**.



Scheme 1.22

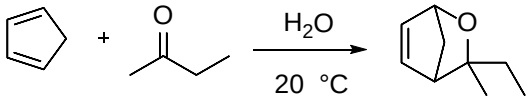
35 is themally stable and shelf stable, and has been used successfully as a diazo transfer for a range of active methylene compounds, such as β-ketoesters, ketones and sulfoxides, in excellent yields (83-94%) in less than 5 minutes. Extraction into hexane-ethyl acetate gives pure diazo compound without the need for chromatography.

1.3 Alternative solvents for diazo transfer

1.3.1 Water as solvent for diazo transfer

Since Anastas and Warner reported their 12 Principles of Green Chemistry in 1998,[56] there has been a surge in interest in water as a solvent for organic synthesis. In recent years, a number of reviews have been published examining the use of water as a viable solvent for organic reactions.[57–63] Water has many environmental and economic advantages over traditional organic solvents as it is a cheap, readily available solvent which is non-toxic and non-flammable. Although there are sometimes issues with low solubility of organic compounds in water, it has unique properties which are advantageous to many reactions. These include polarity, ability to form hydrogen bonds, and hydrophobic and hydrophilic interactions.

The emergence of water as a solvent for organic reactions can perhaps be credited to the work of Breslow.[64] The author reported a substantial increase in the rate of Diels-Alder reactions carried out on water versus a range if other organic solvents. The cycloaddition of butanone **37** and cyclopentadiene **36** in water was found to be 740 times faster than in isooctane, and had increased selectivity, illustrated in **Scheme 1.23**. The same reaction was carried out in the polar protic solvents methanol and ethanol, and these were found to have similar reaction rates to the other hydrocarbon solvents used. This result was rationalised by the hydrophobic effect[65] – which is the observed tendency of non-polar substances to aggregate in water and exclude water molecules.[66]

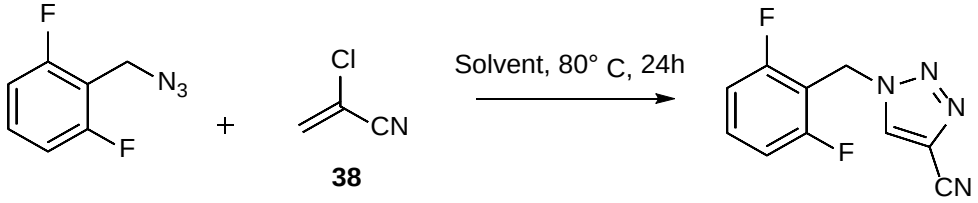


36 **37**

Solvent	k ($M^{-1}s^{-1}$)
Isooctane	5.94×10^5
MeOH	75.5×10^5
H_2O	4400×10^5

Scheme 1.23

Novartis have used water as a solvent in their synthesis of 1-substituted-4-cyano-1,2,3-triazoles.[67] This synthesis involves the 1,3-dipolar cycloaddition of 2-chloroacrylonitrile **38** and the appropriate organic azide, which is followed by an aromatization which generates hydrogen chloride as a side-product. 2-Chloroacrylonitrile **38** polymerises under acidic or basic conditions. Therefore, by using water as a solvent, the reaction could take place in the organic phase while the by-product was solubilised in the water, thus giving higher yields of the product, as shown below in **Scheme 1.24**.

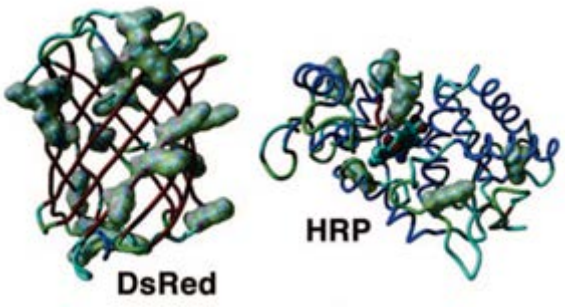


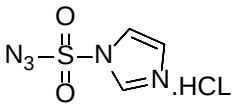
38

Solvent	Yield (%)
n-Heptane	46
Toluene	51
Dimethylformamide	78
Ethanol	40
Neat	72
Water	98

Scheme 1.24

Water has found widespread applications as a reaction medium, and has successfully been used to carry out Claisen rearrangements,[68] aldol reactions,[69] and allylation reactions.[70–72] The only example in the literature of diazo transfer in water was reported by van Heist *et al*.[73] The authors used imidazole-1-sulfonyl azide hydrochloride **25** in aqueous solution to carry out diazo transfer to amines, in order to directly introduce azides at the lysine positions or *N*-terminus of proteins and enzymes (**Figure 1.5**).



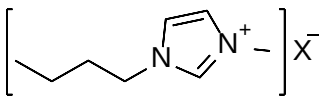


25.HCl

Figure 1.5 Reproduced from Ref 74.

1.3.2 Ionic liquids as solvent for diazo transfer

Ramachary and co-workers described the use of ionic liquids as reaction solvent for diazo transfer.[55] The ionic liquids chosen were 1-butyl-3-methylimidazolium (bmim) salts which can be reused for up to five runs without affecting reaction rates or yields (**Figure 1.6**).



X= BF_4 **39**, OH **40**, Br **41**

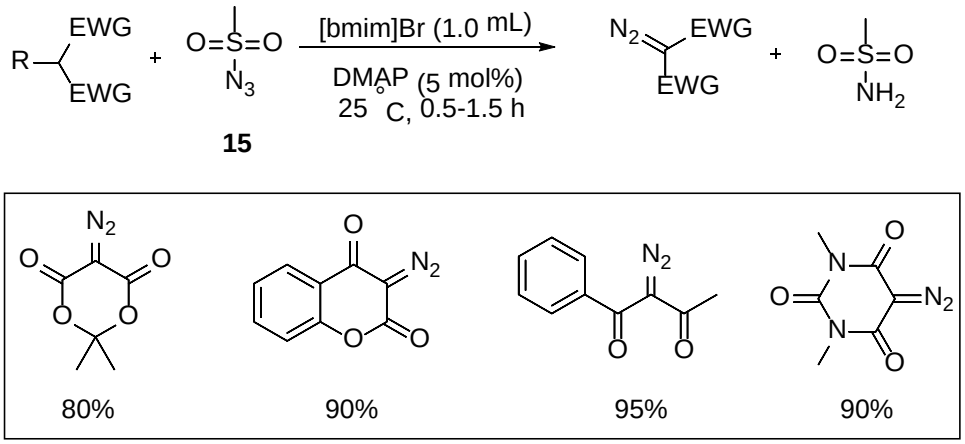
Figure 1.6

A range of highly substituted symmetrical and unsymmetrical α-diazoketones and α-diazo esters were prepared using a variety reaction conditions. Multiple sulfonyl azides and various bases were used during optimisation, as well as two different ionic liquids: [bmim]BF_4 **39** and

[bmim]Br **41**. The authors reported that these reactions are successful in the absence of a base, but the presence of a catalytic amount of base serves to accelerate the reaction. The optimum reaction conditions were found to be as follows:

- 1 equivalent of methanesulfonyl (mesyl) azide **15**
- 5 mol% DMAP
- [bmim]Br **41** (1 mL)

Using these reaction conditions, diazo transfer to a wide range of substrates was achieved in very short reaction times (0.5 – 2h), as illustrated in **Scheme 1.25**.



Scheme 1.25

1.4 Diazo chemistry in continuous processing

1.4.1 Advantages and limitations of flow chemistry

Perhaps the greatest challenge in organic synthesis is to generate complex organic compounds from simple precursors. This is accomplished *via* multi-step synthesis, often with each step requiring purification and optimisation before being carried on to the next stage of the reaction. Although working in this manner is the foundation on which modern synthesis has been built, a new method which proposes to increase efficiency, decrease exposure to hazardous and toxic intermediates and offers new opportunities for easy scalability has emerged.

Flow chemistry has emerged in recent years as a safer, more economical route by which to carry out organic synthesis. Flow chemistry could be viewed as a better mirror to the single-

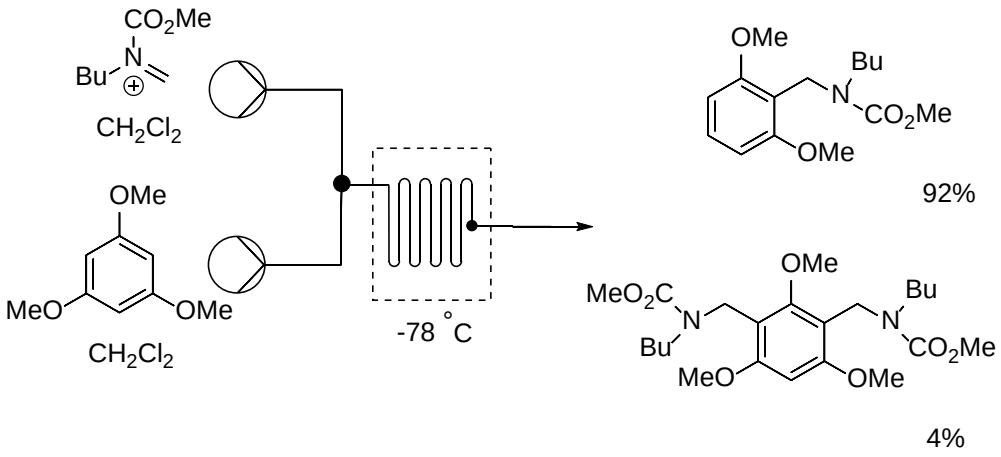
cell multi-step biosynthetic pathways found in nature than traditional batch chemistry. Numerous reviews exist in the literature on the advantages of flow chemistry, which are outlined below.[74–84]

Reported advantages of flow chemistry include the following[80]:

- Controlled heat transfer
- Controlled mixing (both fast and slow)
- Increased photon-flux in photochemical reactions
- Increased electrode surface-to-reactor volume ratio (electrochemistry)
- Increased solution-solid phase interactions
- Controlled use of highly reactive/toxic materials
- Increased capacity to run serial reactions.

The tunability of flow reactors, and the fact that reactions take place in small diameter tubing or microchips allows reactions to be performed under a more extensive range of conditions than can be achieved with conventional reactors. The excellent heat/mass transfer capabilities that this affords in comparison to batch chemistry leads to faster reaction times, high reproducibility and superior overall yield when compared to the stepwise process.[81] In addition, continuous processing allows for rapid scale up of reactions without the significant redevelopment of the routes that are frequently required on scale-up of batch processes.[78] This is achieved by replication of the same microreactor conditions used in the laboratory, but on an industrial scale. This can shorten the development time from laboratory to final production levels by eliminating the need for redevelopment from laboratory to pilot plant, and from pilot plant to industrial scale.[77]

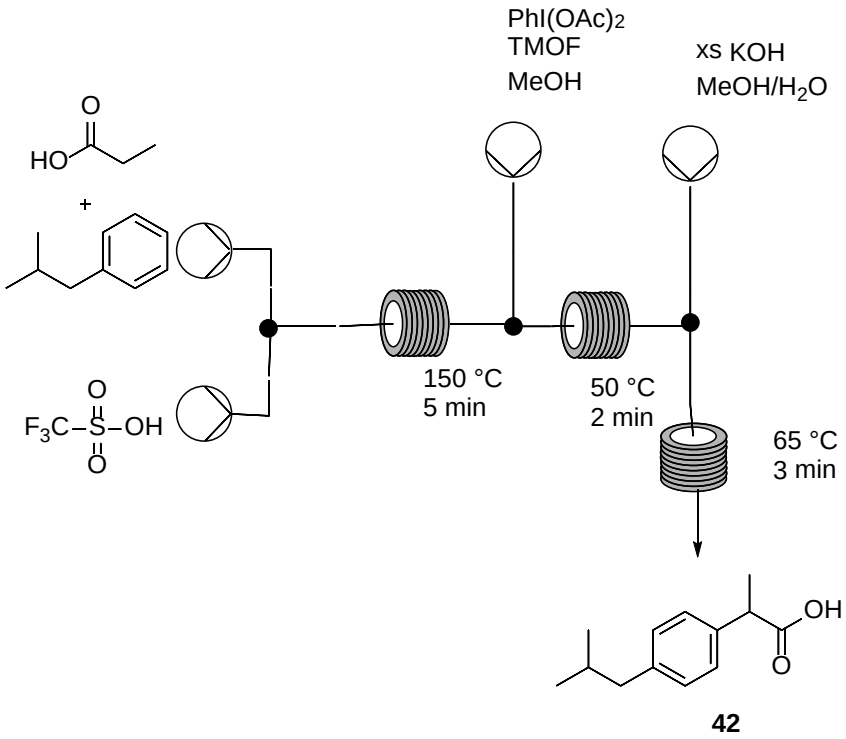
Jensen *et al*. reported an example of the effects of improved mixing in continuous flow processes.[79] In this example fast mixing eliminated the competitive formation of the dialkylated product, thus increasing yields of the desired monoalkylated product from 36% in batch to 92% in flow (**Scheme 1.26**).



Scheme 1.26

Perhaps one of the most significant advantages of continuous processing is the ease with which telescoped reactions can be carried out. To perform a telescoped reaction in batch, the chemist would typically be required to consecutively add reagents and/or catalysts to a reactor in order to initiate further transformations of intermediate products or to achieve *in situ* quenching of reactive species. This strategy is well suited to flow chemistry.[82]

In telescoped reactions in flow, intermediates can be generated in one reactor and then transferred to another reactor to react with additional reagents. Immobilized reagents are used to perform in-line quenching and scavenging of by-products that would traditionally be performed by aqueous work ups and/or column chromatography.[80] This allows the chemist to carry out "one-flow multi-step synthesis" that would previously have required isolation and purification between steps.[85] Bogdan *et al*. made use of this concept when developing a three-step telescoped synthesis of ibuprofen **42**, as shown in **Scheme 1.27**.[86] By designing a careful retrosynthetic analysis of ibuprofen the authors were able to design the synthesis such that any by-products and excess reagents from one reaction were compatible with downstream reactions. This meant that the three step synthesis could be carried out as one sequence without any breaks for purification.

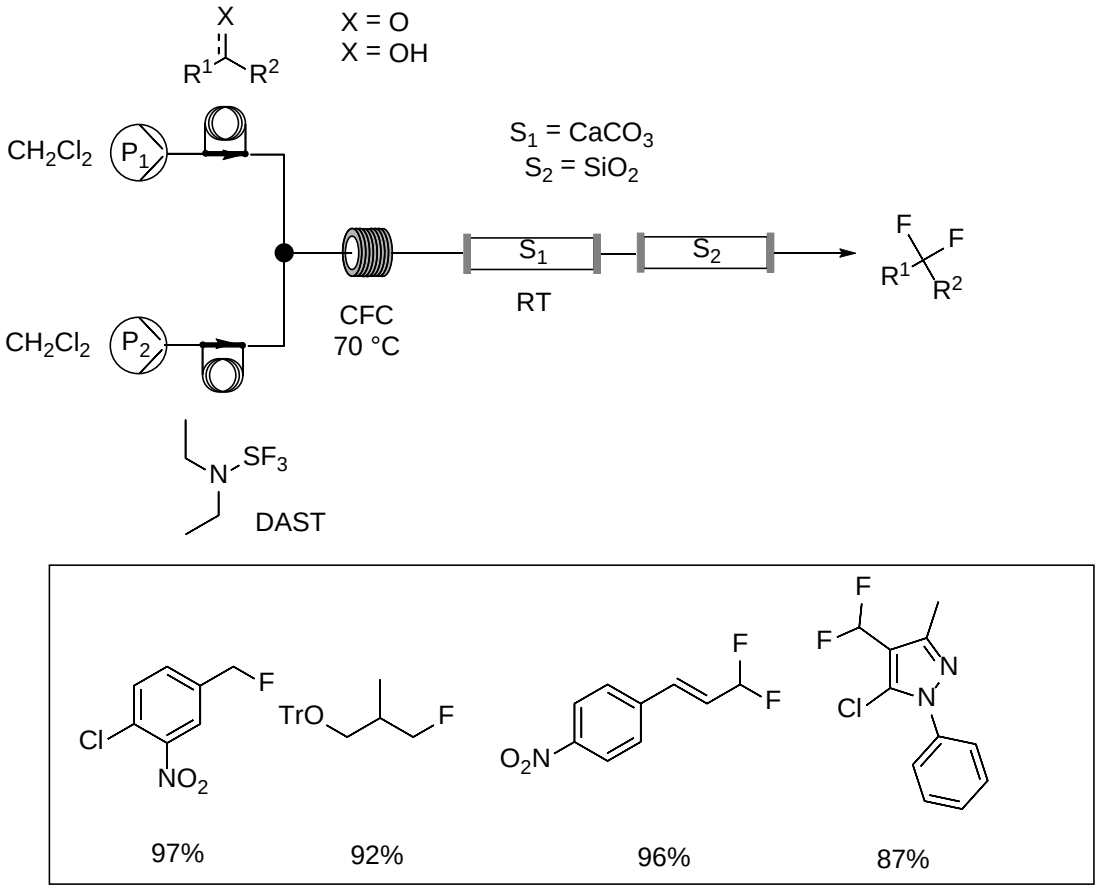


Scheme 1.27

In a continuous process, reagents are pumped into a flow reactor separately, before meeting at a T-piece. This means that at any one time, a small volume of reagents are in contact with each other. This is especially important when the intermediates being formed are hazardous, toxic or volatile.[78] As the system is closed, the chemist is never in contact with any toxic reagents, and the potential for problems with highly reactive or explosive reagents is significantly reduced.[77] It also allows the chemist to isolate and use compounds sensitive to air and/or moisture.[81] Flow chemistry employs a 'make and use' concept,[77] which means that any unstable or dangerous intermediates are generated and then rapidly transferred to the next stage of the reactor to be consumed, before decomposition or other problems can occur. This further increases the safety profile of the flow process.

An application of this is seen in reports by Baxendale and co-workers.[77] Diethylamino sulfur trifluoride (DAST) is volatile, reacts violently with water and readily decomposes at temperatures above 90 °C; as such it is difficult to use in batch. However the authors successfully used it in a continuous flow process to carry out fluorination reactions – DAST

provides rapid access to many chemical structures by replacement of alcohols or carbonyl groups with mono- or *gem* difluoro groups, as shown in **Scheme 1.28**.



Scheme 1.28

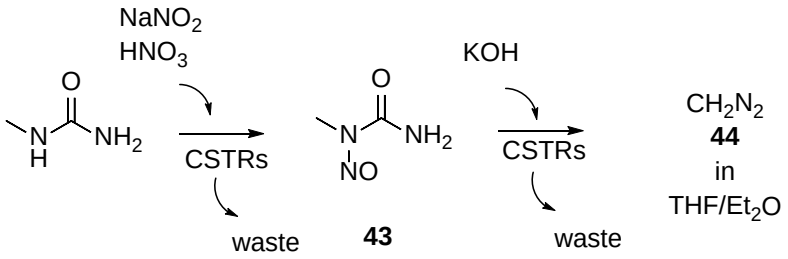
Continuous processing is not without its disadvantages. Homogenous solutions are extremely important when carrying out flow chemistry, as due to the nature of the small diameter tubing in the reactor, any precipitate reagents will quickly clog the lines and lead to system failure from pressure elevated above the operating limits.[79]

Reaction planning is key in the use of flow reactors. Understanding the chemistry being performed, and identification of all by-products is critical in effective experiment design, therefore downstream post reaction clean-up is essential.[82] Effective quenching mechanisms must be put in place for any hazardous or toxic intermediates, as well as a method of removing by-products if possible. An added challenge is ensuring downstream reagent compatibility. Solid supported reagents are extremely useful for these purposes, but they too have limitations regarding volume and scaling (pressure effects and reactor volumes).[77,82]

1.4.2 Generation of diazomethane using continuous flow technology

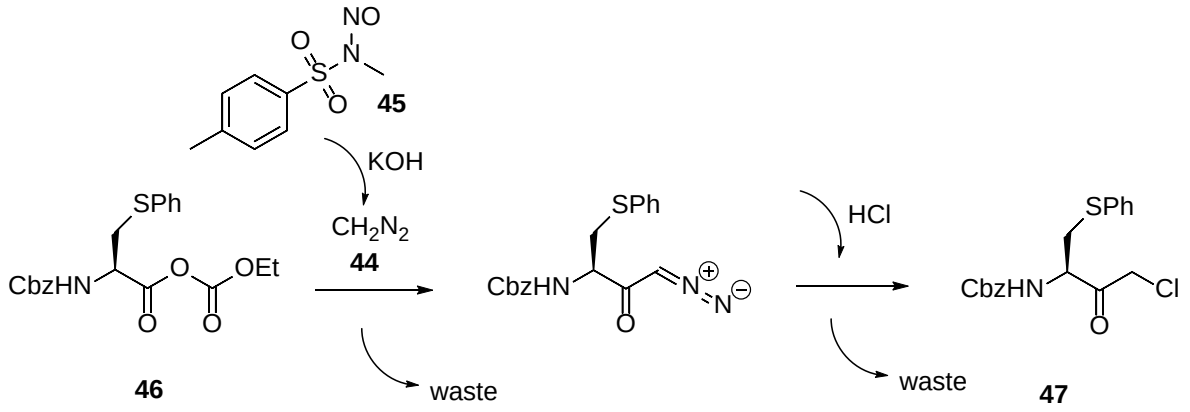
Diazomethane **44** is a powerful carcinogen and allergen and is highly toxic with a permissible exposure limit of 0.2 ppm averaged over an 8-h period. However, the biggest impediment to its use on an industrial scale is very high sensitivity to shock and heat. The explosive nature of **44** is such that its batch synthesis must be carried out in specialised vessels without ground glass joints. There have been several methods reported for generating diazomethane in small quantities at a laboratory scale using flow reactors,[87–90] however the real challenge lies in safely generating and using industrial scale quantities. Several reported methods are outlined below.

The first company to publish methods capable of generating truly large volumes of diazomethane is Aerojet General Corporation.[91] This process generated **44** in ethereal solution from decomposition of *N*-nitroso-*N*-methylurea **43** by addition of aqueous KOH reagent stream, illustrated below in **Scheme 1.29**. The process used a series of continuously stirred tank reactor (CSTR) stages, and was capable of providing a continuous supply of 61 mol h^{-1} of diazomethane in THF/ether.



Scheme 1.29

Proctor and Warr of Phoenix Chemicals reported the synthesis of diazomethane on an industrial scale.[92] In this synthesis, diazomethane **44** is continuously generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonyl amide (**45**, Diazald®). A continuous stream of **45** is subjected to an aqueous KOH feed, generating diazomethane which is then extracted into the gas phase by subsurface and headspace flows of nitrogen gas. The nitrogen flow then carried the diazomethane into a solution containing substrate **46** to generate α-chloroketone **47** (**Scheme 1.30**).



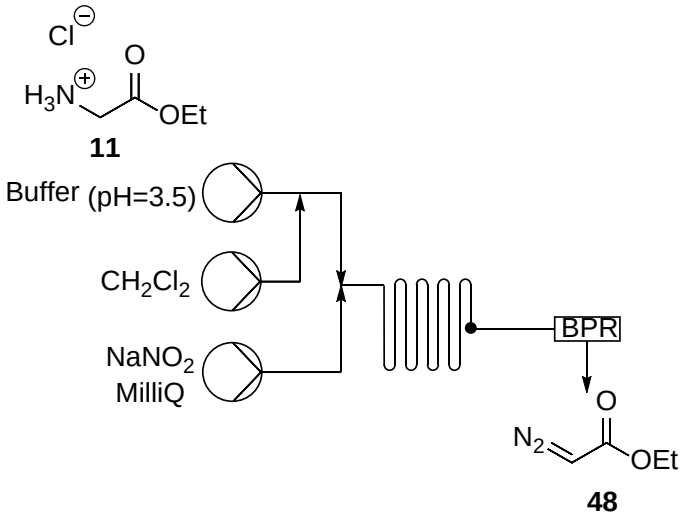
Scheme 1.30

The synthesis and the plant designed to run the process was capable of producing 60 metric tonnes of **44** per year, and operated safely for several years. A large number of safety features were incorporated into the plant such as in-line monitoring of **44**, secondary fail safe monitoring, automated shutdown, as well as a procedure for the worst case scenario – the reactor contents would be quenched automatically in the case of a reactor burst failure. Due to the need for decomposition by KOH, this synthesis is unsuitable for base-sensitive compounds.

1.4.3 Preparation of ethyl diazoacetate using continuous flow technology

Ethyl diazoacetate **48** is another important diazo-based reagent. It is used in the cyclopropanation of alkenes. **48** is a highly explosive reagent, and must be produced in a contained manner.

Rutjes *et al*. studied the formation of ethyl diazoacetate **48** from glycine ethyl ester hydrochloride **11** with sodium nitrite, as shown below in **Scheme 1.31**.[93] They effectively optimized the temperature, residence time and quantities of sodium nitrite being used to provide a process capable of delivering up to 175 mmol ethyl diazoacetate **48** per day using a microreactor with an internal volume of 100 µL. The authors postulated that with scale-up this method is viable for industrial application.



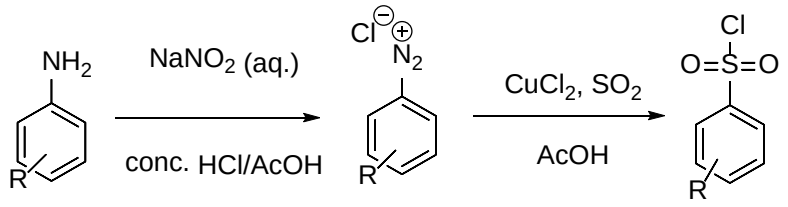
Scheme 1.31

Other laboratory-scale syntheses of ethyl diazoacetate **48** using continuous flow methods have been reported in the literature,[94,95] however there is little in the literature concerning industrial scale synthesis. Poechlauer and co-workers from DSM Pharmaceuticals have synthesised and applied both diazomethane and ethyl diazoacetate in continuous flow systems for plant-scale processes.[96]

1.4.4 Diazonium ions in flow

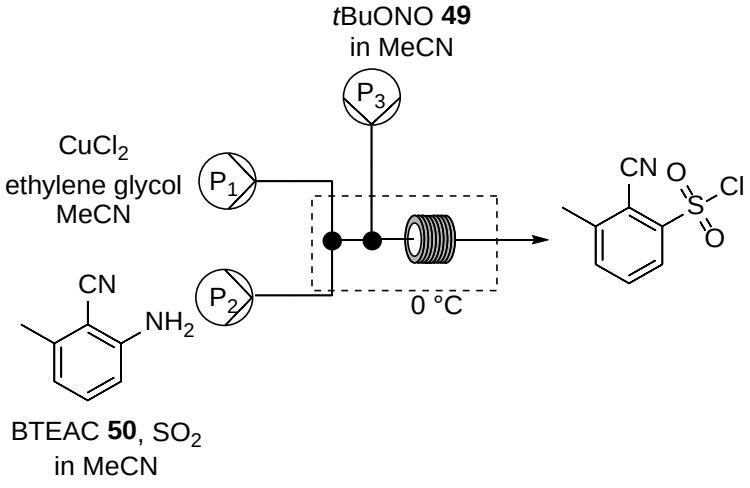
Diazonium salts can be very explosive: the stability of the salt is closely linked with the counter-ion. Diazonium halides are often dangerously explosive and have to be generated and used *in situ*. They are unstable above 0 °C and so must be used below this temperature. Diazonium salts with weakly coordinating counter-ions such as tetrafluoroborates, tosylates and disulfonyl amides are quite stable.[97,98] There are several examples in the literature of the generation and use of diazonium salts using continuous flow technology.[99–104]

Ley and collaborators at Pfizer have reported a variation of the Sandmeyer reaction which allows them to access sulfonyl chlorides from anilines *via* diazonium salts.[105] The classical reaction was first reported by Meerwein and co-workers.[106] This variation of the Sandmeyer reaction converted anilines to diazonium salts by reaction with sodium nitrite in a mixture of conc. HCl and acetic acid (**Scheme 1.32**). The corresponding sulfonyl chlorides can then be prepared.



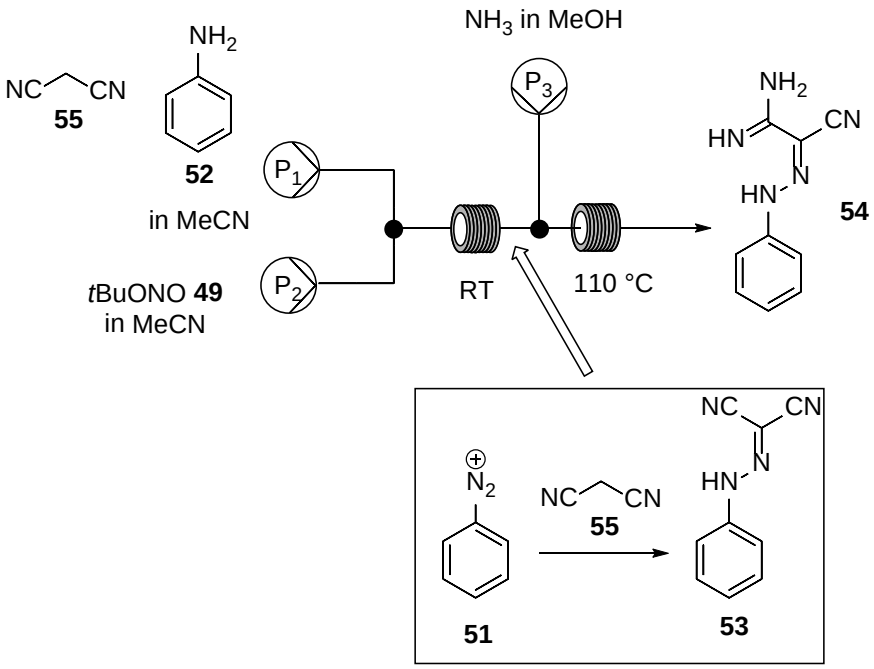
Scheme 1.32

Ley *et al*. aimed to generate diazonium ions in a continuous flow to form the sulfonyl chlorides. A number of adjustments to the original reaction conditions were necessary in order to make the process amenable to a flow process. Concentrated hydrochloric acid and acetic acid is not suitable for use in a flow reactor due to issues associated with corrosion of the stainless steel components in the pumps. The formation of precipitates was a major issue, causing blockages in the reactor. It was decided to use *t*-butyl nitrite **49** in place of sodium nitrite, which allowed use of benzyltriethylammonium chloride (BTEAC) **50** as an alternative source of chloride to hydrochloric acid. Ethylene glycol was used to solubilise $CuCl_2$ in acetonitrile. By implementing these changes, illustrated in **Scheme 1.33**, the authors were able to design a successful flow synthesis for arylsulfonyl chlorides.



Scheme 1.33

Jacq *et al*. have reported the synthesis of diazonium salts as part of a telescoped synthesis of 2-substituted [1,2,3]-triazoles.[107] The diazonium salt **51** is formed by reaction of aniline **52** with *t*-butyl nitrite **49** in acetonitrile. The 2-arylhydrazonoomalononitrile intermediate **53** was then reacted with ammonia to produce 2-arylhydrazonoacetamidine **54** in good yields (>4g in 6.25h), as can be seen in **Scheme 1.34**.



Scheme 1.34

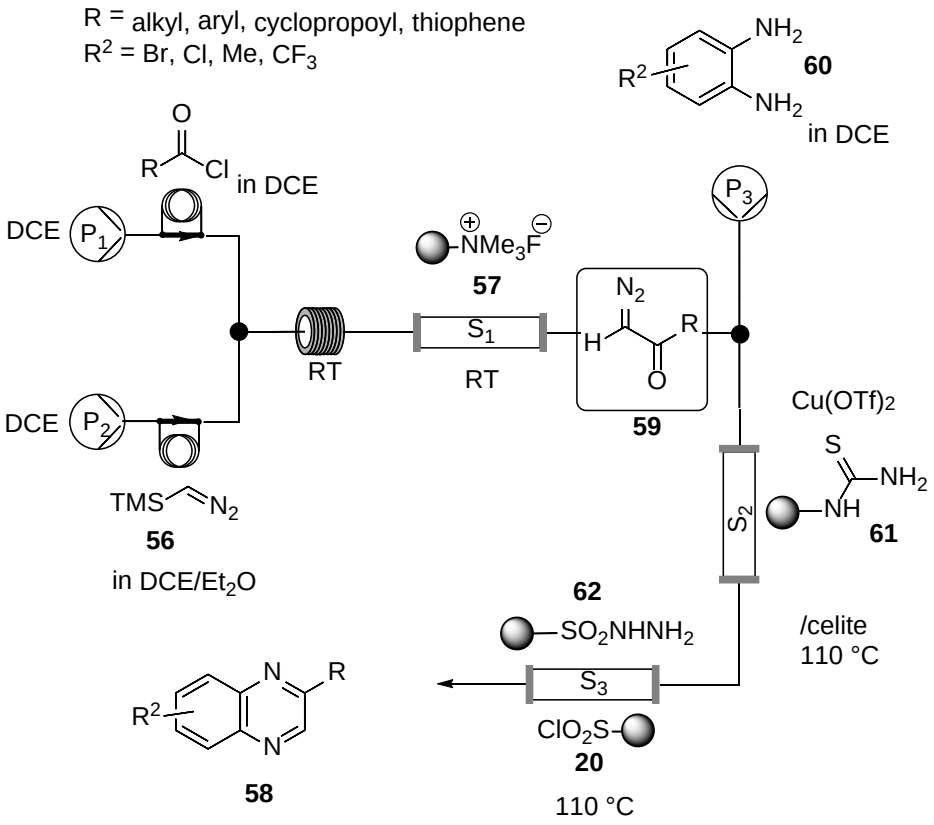
1.4.5 α-Diazocarbonyl compounds in flow

α-Diazocarbonyl compounds are generally stable compounds, however the reagents used to generate them can be very shock and temperature sensitive, making them unsuitable for use on an industrial scale.[5,10] Various syntheses have been published making these versatile compounds in flow.[94,95,108–111]

Ley and collaborators at Novartis have reported generation and telescoped use of diazoketones from acyl chloride precursors.[109] The authors employed trimethylsilyldiazomethane ($TMSCHN_2$) **56** as a safer alternative to diazomethane **44**. **56** is more thermally stable than **44**, but is still toxic and therefore requires care when handling. A range of aliphatic, aromatic and heteroaromatic diazoketones were generated by reaction of

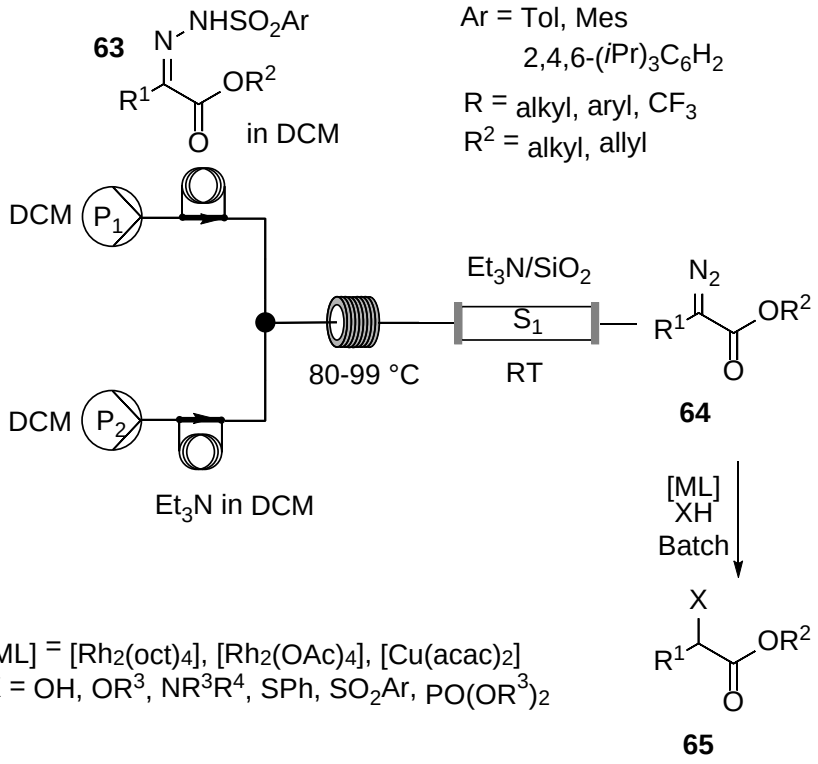
acyl halides and $TMSCHN_2$ **56** in dichloroethane (DCE). PS-tetraalkylammonium fluoride salt **57** was found to work well as both base and impurity scavenger for this stage of the reaction.

Once the diazoketones had successfully been synthesised, it was decided to attempt to use them in the synthesis of interesting heterocycles, e.g. quinoxalines **58**. Diazoketone **59** was reacted with suitable 1,2-diaminobenzenes **60**. The authors chose to make use of PS-scavengers to purify the reaction stream in an attempt to carry out quinoxaline synthesis in a single telescoped flow sequence. PS-thiourea **61** was used to scavenge any dissolved metal salts. PS-tosylchloride **20** captured any unreacted diamine, and PS-tosylhydrazine (PS-$TsNHNH_2$) **62** was used to scavenge residual diazoketone. In this manner an efficient, rapid and safe process for the generaton and use of diazoketones in a telescoped synthesis of quinoxalines **58** was developed, which is shown in **Scheme 1.35**.



Scheme 1.35

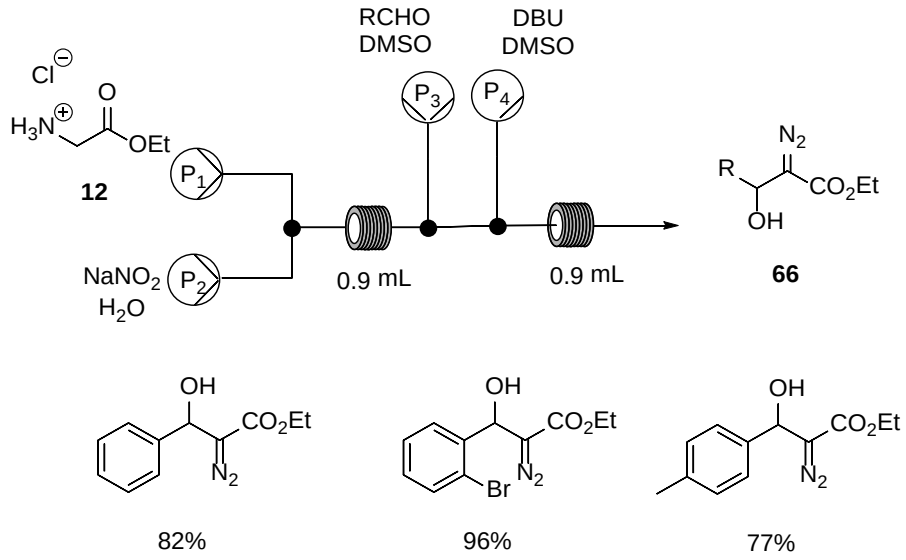
Bartrum and co-workers employed a Bamford-Stevens type reaction to synthesise α-diazoesters as part of a two-step process to generate a range of different α-alkoxy and α-amino acid derivatives, illustrated below in **Scheme 1.36**.[110] This was achieved by decomposition of arylsulfonylhydrazones **63**, with the sulfinic acid by-product being trapped by a Et_3N/silica gel scavenger column. Addition of a 250 psi back-pressure regulator (BPR) in line after the scavenger column allowed safe superheating of the hydrazones to their corresponding α-diazoesters **64**.



Scheme 1.36

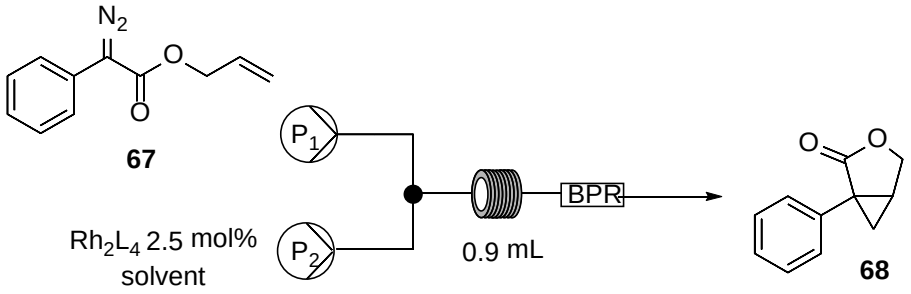
The α-diazoesters were then collected and used in O-H and N-H insertion reactions in batch mode, to form a range of α-alkoxy and α-amino acid derivatives. The authors later reported S-H and P-H insertion reactions using the same hybrid flow-batch methodology.[111]

Wirth *et al*. reported the generation of α-diazo-β-hydroxy esters using continuous processing.[95] This was achieved by *in situ* generation of ethyl diazoacetate and subsequent reaction with the appropriate aldehyde as shown in **Scheme 1.37**.



Scheme 1.37

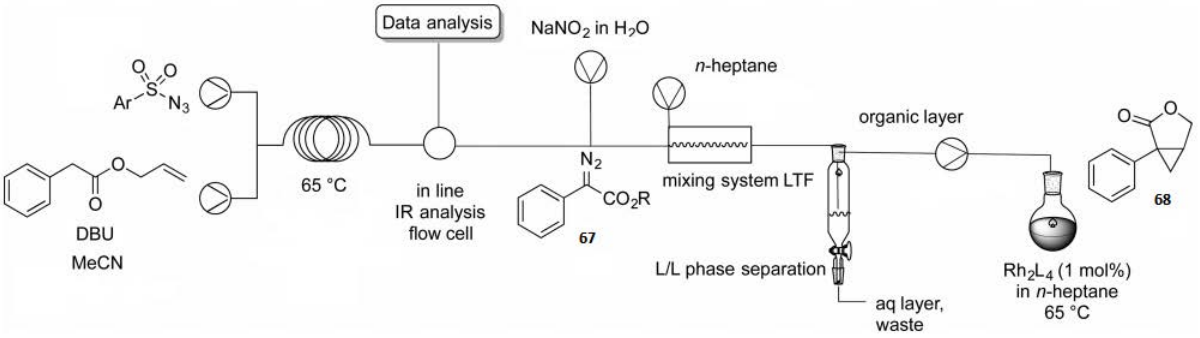
Wirth and co-workers also published a telescoped synthesis of bicyclic lactones such as **68** *via* diazoesters.[112] The authors first optimized the rhodium(II) catalysed decomposition of diazoesters (**Scheme 1.38**), a range of which were also prepared in flow. The rhodium(II) catalysts were suspended in various solvents and combined with the diazoesters at a T-piece. A back-pressure regulator is required when using a solid reagent suspended in a solvent, due to the potential for clogging of the lines, as discussed in **Section 1.5.1**. Due to issues of solubility of the catalysts, it was decided that the intramolecular cyclopropanation under continuous flow conditions was not suitable for scale-up.



Scheme 1.38

The complete telescoped synthesis of the bicyclic lactone **68** is shown in **Scheme 1.39**. The authors used in-line IR analysis to confirm the formation of **67** before the continuous stream

is directed into a unique in-line liquid-liquid extraction. A stream of the diazo compound in the organic layer was directed into a flask containing the rhodium catalyst in *n*-heptane to produce the desired product **68**. This method was successfully scaled-up to gram quantities, however a reduced yield was obtained. Although this is a semi-batch protocol, it avoids the need for column chromatography of the diazo reagent.

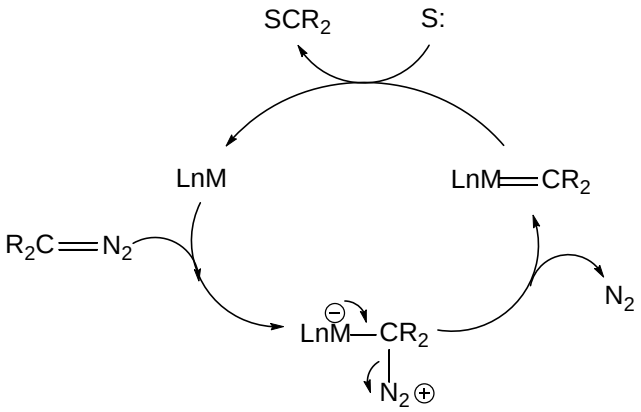


Scheme 1.39 Reproduced from Ref 113.

1.5 Reactivity of α-diazocarbonyl compounds

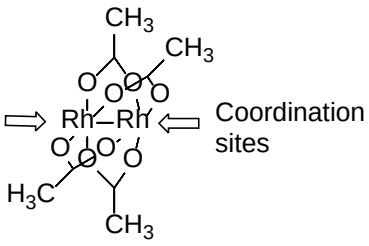
1.5.1 Mechanism of transition metal catalysed decomposition

The widely accepted mechanism for diazocarbonyl decomposition is shown in **Scheme 1.40**.[6,113,114] This has been confirmed using computational studies by Nakamura and co-workers.[115] The first step is electrophilic addition of the diazocarbonyl compound to the transition metal, followed by nitrogen extrusion. This results in the formation of a metal stabilised carbene, which is then transferred to an electron rich substrate (S:) to complete the catalytic cycle. The transition metal catalysts effective in the decomposition of α-diazocarbonyl compounds are essentially Lewis acids, which have an empty molecular orbital into which the electrophilic carbene can donate electrons.[3]



Scheme 1.40

Copper catalysts were the predominant catalyst for decomposition of α-diazocarbonyl compounds for almost 70 years, until Teyssie introduced rhodium(II) acetate for the same purpose in 1973.[1,2] Rhodium(II) acetate **69** (**Figure 1.7**) is a binuclear compound, with four bridging acetate ligands and D_{4h} symmetry.[116,117] It possesses one vacant axial coordination site per metal atom.

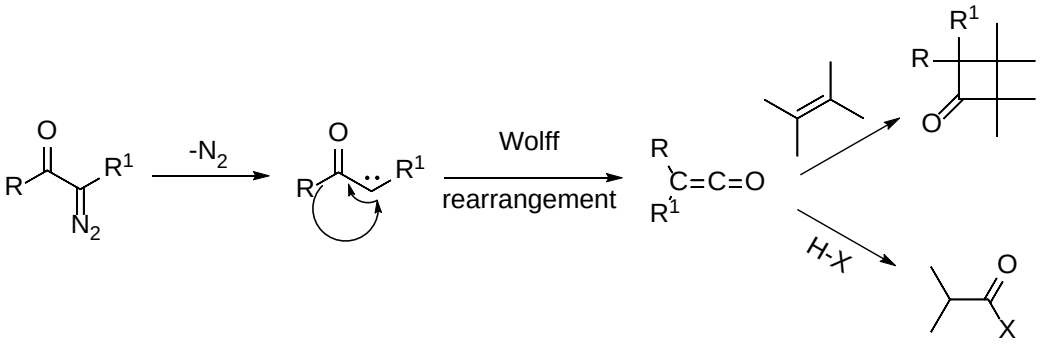


$Rh_2(OAc)_4$
69

Figure 1.7

1.5.2 Wolff rearrangement

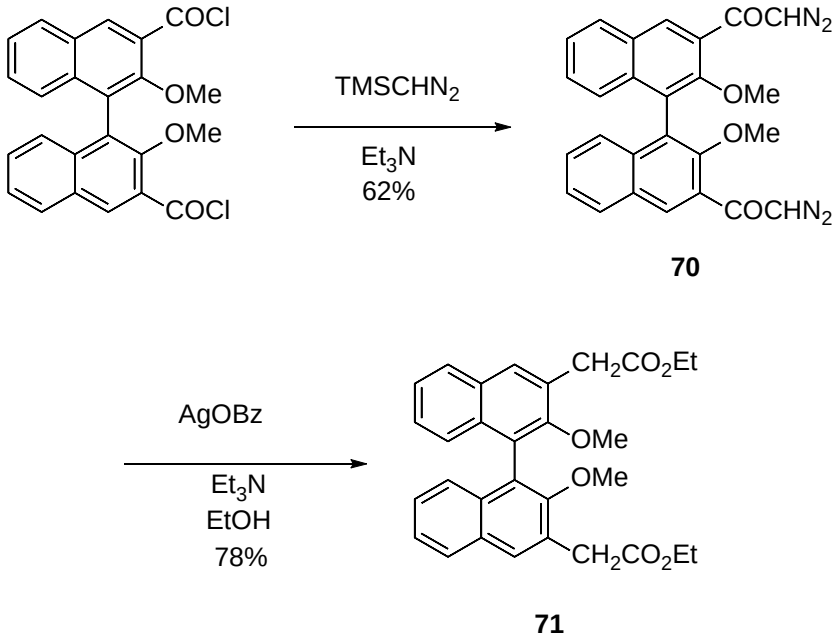
The Wolff rearrangement was first reported by Ludwig Wolff in 1902, and has since become a widely used synthetic pathway.[118] Many reviews have been published concerning this rearrangement,[119–122] the most comprehensive of which is a 100 year overview by Kirmse.[123] It is a 1,2-rearrangement of diazoketones, initiated by the loss of nitrogen, to form a ketene which may undergo further reactions with nucleophiles or cycloadditions to unsaturated systems (**Scheme 1.41**).



Scheme 1.41

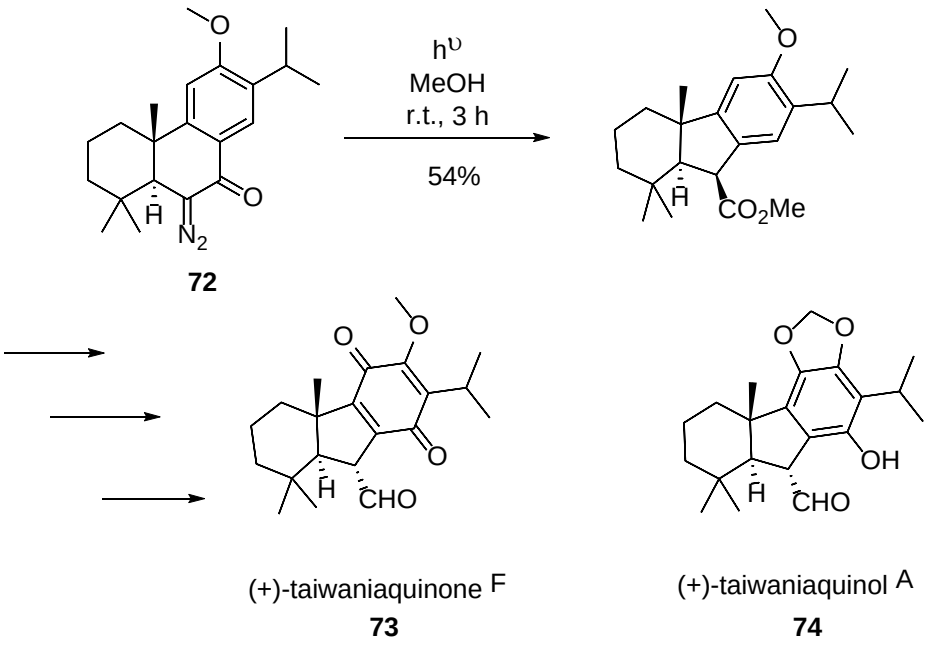
The Wolff rearrangement can be initiated by thermolysis, photolysis, or metal ion catalysis. The widely accepted mechanism is viewed as concerted, although much evidence for a stepwise mechanism *via* formation of reactive carbonylcarbenes has been derived from various matrix-isolation studies and low-temperature time-resolved spectroscopy.[124–129]

The most common application of the Wolff rearrangement is the Arndt-Eistert synthesis, which is a one-carbon homolgation of carboxylic acids using diazomethane.[130] Hundreds of variations on the original paper have been published to date, including the example shown below in **Scheme 1.42**.[131] The reaction of a bis(acid chloride) with diazomethane failed to give reproducible results. By using (trimethylsilyl)-diazomethane instead, the authors were able to successfully produce diazoketone **70**, which could be converted to diester **71** in the presence of silver benzoate in ethanol.



Scheme 1.42

The Wolff rearrangement also has applications in natural product synthesis. Thommen *et al*. reported the use of a Wolff rearrangement to give ring contraction as a crucial step in the total syntheses of taiwaniaquinone F **73** and taiwaniaquinol A **74**.[132] This photolysis mediated rearrangement of the diazo derivative of sugiol methyl ether **72** yielded the unusual 6-5-6 ring system associated with taiwaniaquinoids.

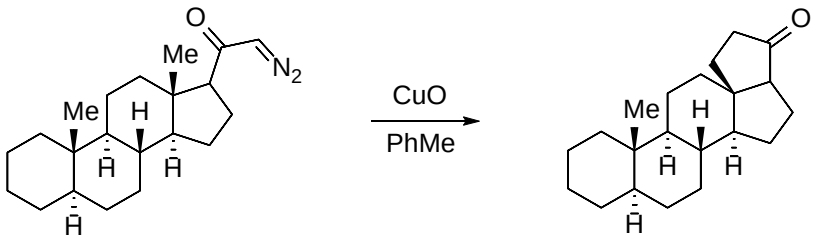


Scheme 1.43

1.5.3 C-H insertion reactions

Carbene insertion into C-H bonds is an important synthetic reaction. Hundreds of examples of this extremely useful transformation can be found in the literature, and the reaction has been reviewed most recently by Maguire[133] and Doyle.[134] This section will examine the history of its discovery, along with some interesting applications in natural product synthesis.

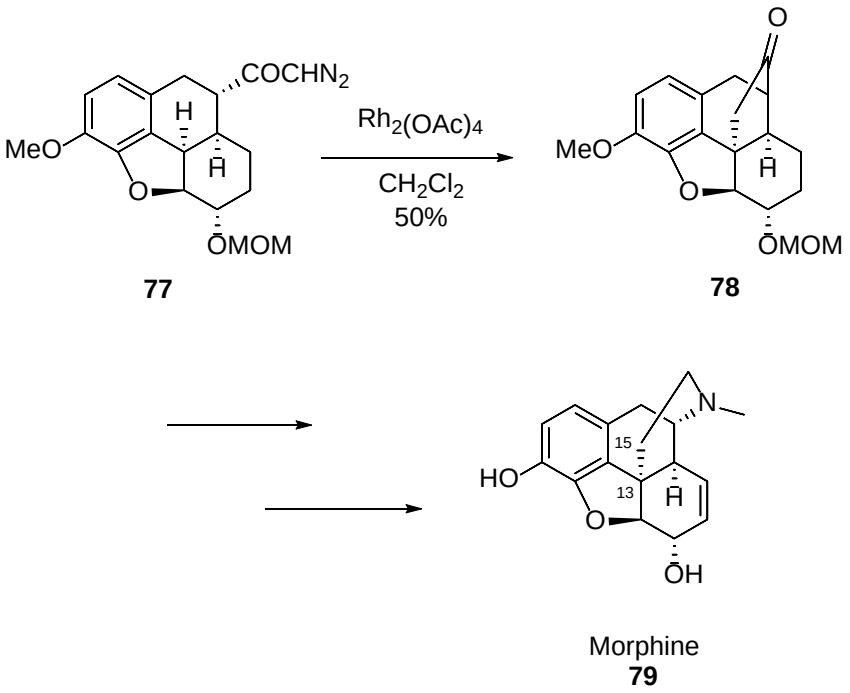
The first report of C-H insertion was a photolysis reaction reported by Meerwein and co-workers.[135] Transition metal catalysed C-H insertion was first reported by Greuter *et al.* as illustrated in **Scheme 1.44**.[136] The authors reported copper mediated generation of a carbene from the corresponding diazoalkane **75**, which underwent C-H insertion to form the cyclopentanone **76**.



75 **76**

Scheme 1.44

The full potential of the C-H insertion reaction was only recognised after Teyssie and co-workers reported the first example of such a reaction catalysed by rhodium(II).[137] Since then, rhodium(II) acetate **69** has become one of the most widely used reagents in diazo chemistry, and is used in various syntheses of natural products. A complete synthesis of the alkaloid morphine **79**, a powerful analgesic, was published by White *et al*. in 1997 that employed an intramolecular carbenoid C-H insertion reaction.[138] Rhodium(II) acetate was used to achieve the transformation from the diazoketone **77** to **78**, establishing a bond from C13 to C15, as shown below in **Scheme 1.45**.



Scheme 1.45

Lloyd and co-workers employed another rhodium(II) catalyst, in their selective C-H insertion reactions for the synthesis of α-methylene-γ-butyrolactone natural products.[139] Dirhodium tetraoctanoate **80** is a rhodium(II) is a binuclear compound, with four bridging octanoate ligands whose structure is shown in **Figure 1.8**.

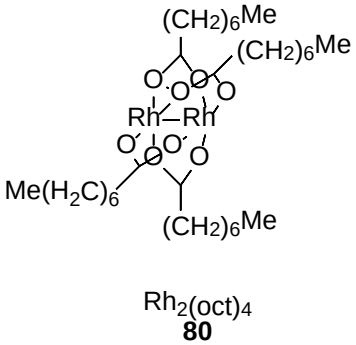
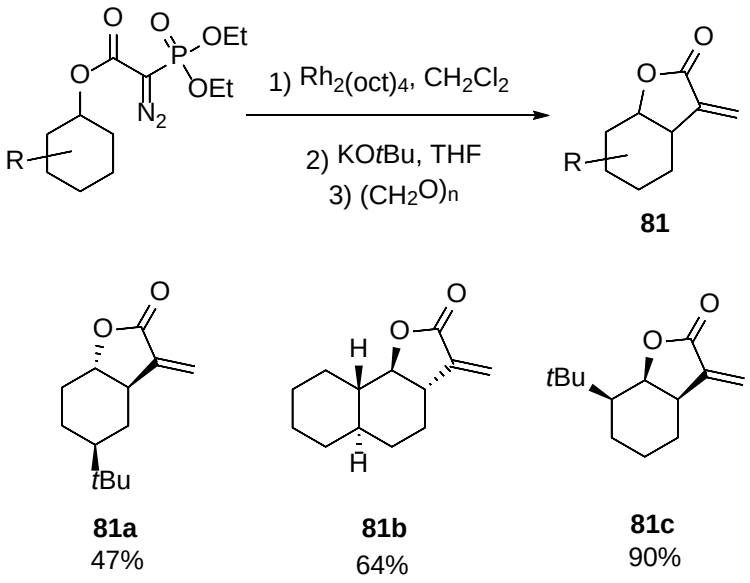


Figure 1.8

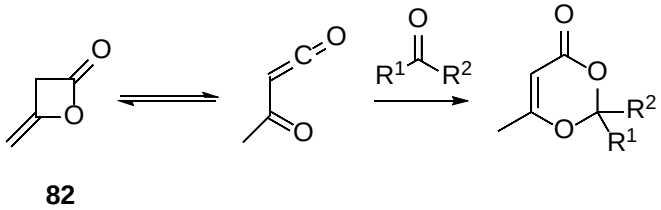
The authors synthesised a range of conformationally restricted cyclohexane derivatives by use of rhodium(II) catalysed decomposition of the corresponding diazophosphonates (**Scheme 1.46**). This method was then used in the synthesis of the natural product, α-cyclocostunolides **81**.



Scheme 1.46

1.5.4 Dioxinones

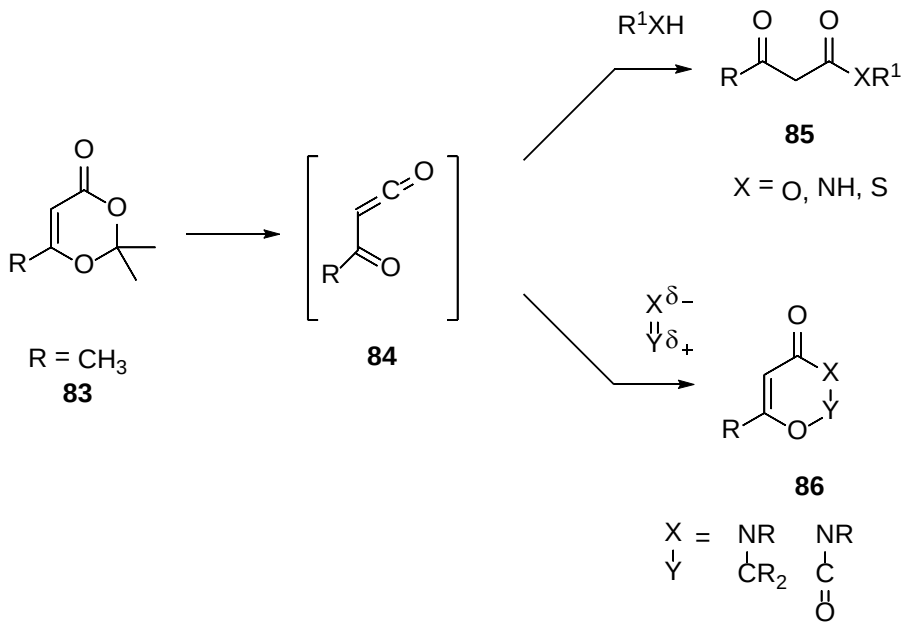
Diketene **82** was first reported by Wilsmore in 1907,[140] but it was not until 1952 that Carroll and Bader reported the reaction of diketene with ketones to form 2,2-disubstituted-4-methyl-6-keto-1,3-dioxinones, as shown in **Scheme 1.47**.[141,142]



Scheme 1.47

The structure of 2,2,6-trimethyl-4H--1,3-dioxin-4-one **83**, the adduct formed by reaction of diketene with acetone, was confirmed using proton magnetic resonance in 1956.[143] Since their discovery, dioxinones have been widely used, and have been reviewed a number of times.[144–147] The following section will outline some uses of dioxinones.

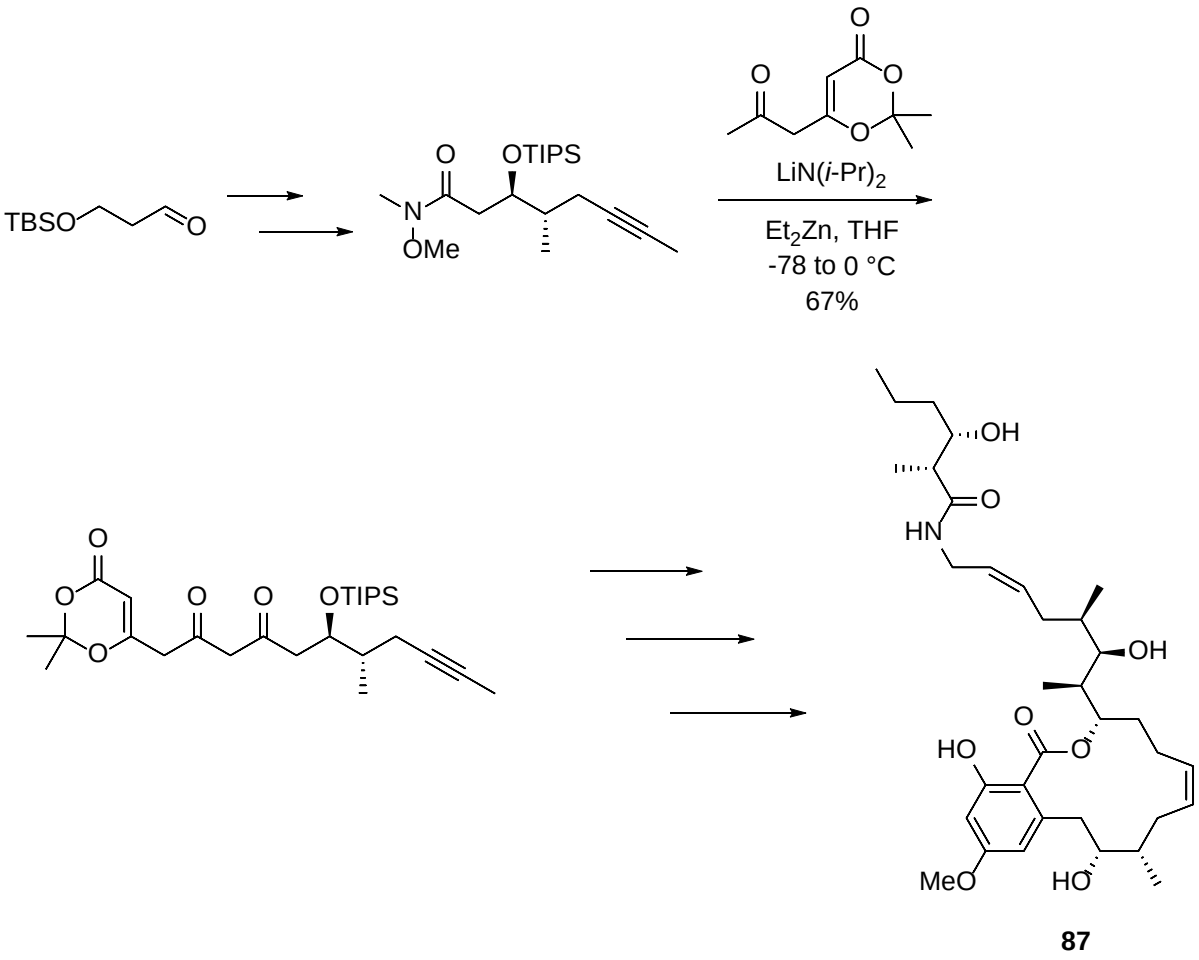
Sato *et al*. reported that dioxinones could be used to form the corresponding acylketenes **84**, which could either react with nucleophiles to give β-keto acid derivatives **85**, or react with dipolarophiles to give six-membered heterocyclic compounds **86**, such as lactones and lactams (**Scheme 1.48**).[144,145,148]



Scheme 1.48

Dioxinones have been used as a key intermediate in the biomimetic total synthesis of resorcylates.[149] Resorcylates are a large group of bioactive natural products, whose bioactivities include anticancer, antimalarial, mycotoxicity, antifungal and antibiotic properties.

Key steps in the synthesis of resorcylate Creuntaren A **87** are shown below in **Scheme 1.49**. Creuntaren A **87** is an antifungal agent that also inhibits the proliferation of different cancer cell lines, including a multidrug-resistant KB carcinoma cell line.[150] This is just one of the resorcylates whose total synthesis was achieved using dioxinones as key intermediates by Barrett and co-workers.[149]



Scheme 1.49

1.6 Lanthanides in organic synthesis

1.6.1 Background

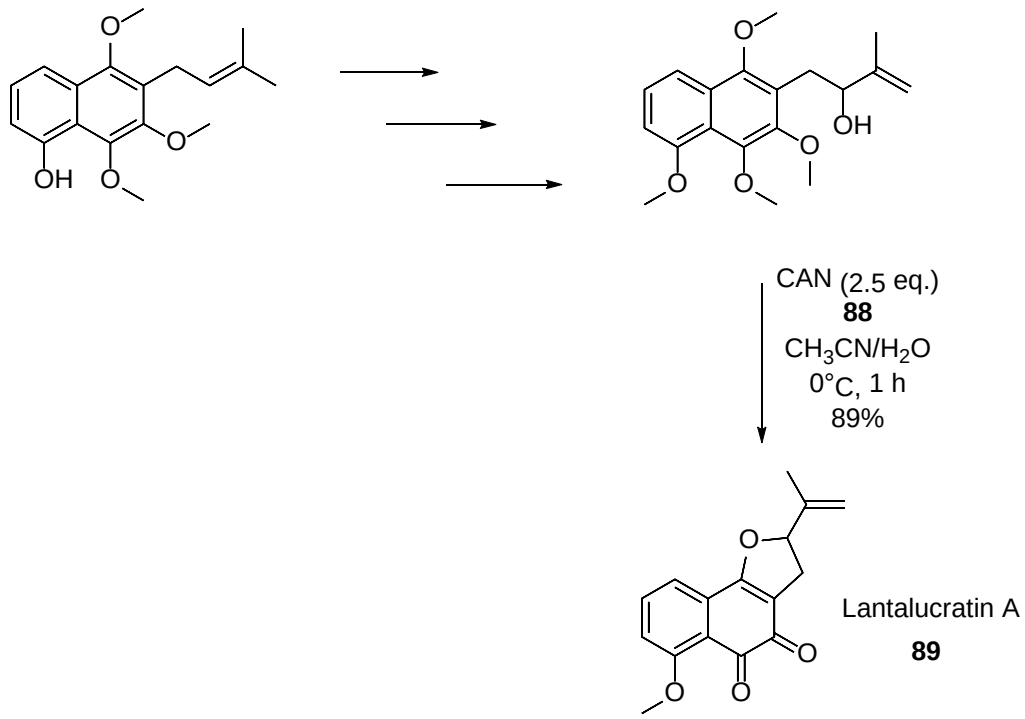
In the 1980s, lanthanide reagents experienced a surge in popularity, with several reviews published on their use in organic synthesis in the intervening years.[152–164] The following is a brief summary of some of the many uses of lanthanide reagents.

1.6.2 Oxidation reactions

Cerium(IV) compounds are powerful one-electron oxidising agents.[164] Ceric ammonium nitrate $(NH_4)_2Ce(NO_3)_6$ **88**, abbreviated as CAN, is perhaps the most widely used reagent in

this class. Cerium(IV) oxidants have been used to oxidise aromatic systems,[165] arenes,[166] alcohols,[167,168] and even α-hydroxy ketones.[169–171]

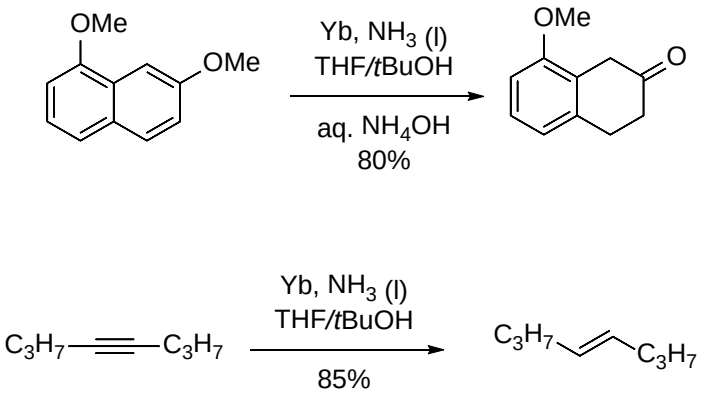
CAN has been used in the total synthesis of (±) Lantalucratin A **89**,[172] a natural product with a naphthoquinone skeleton which has shown cytotoxic activity against various human tumour cell lines.[173] CAN was used to mediate an intramolecular oxidative cyclisation under mild conditions in an excellent yield as the key step in this complete synthesis, as shown in **Scheme 1.50**.



Scheme 1.50

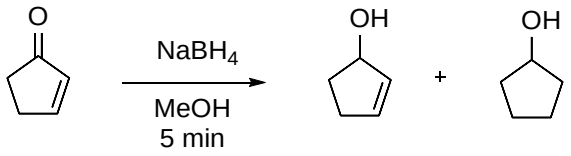
1.6.3 Reduction reactions

The first practical use of lanthanide reducing agents was in the use of ytterbium in liquid ammonia for dissolving metal reductions (**Scheme 1.51**).[174] This is similar to a Birch reduction with alkali metals but has advantages in ease of handling of the metal, and in avoiding the strongly basic hydroxide work up.



Scheme 1.51

Possibly the most well-known use for lanthanide reagents in organic synthesis is the Luche procedure for the selective reduction of conjugated aldehydes and ketones to allylic alcohols.[175–177] The selective 1,2 reduction of enones was first detailed by Luche in 1978, and used sodium borohydride in conjunction with $CeCl_3$, as seen in **Scheme 1.52**. This transformation was not achievable, or proceeded much less efficiently when traditional reducing reagents such as DIBAL, LAH or $NaBH_4$ alone were used.

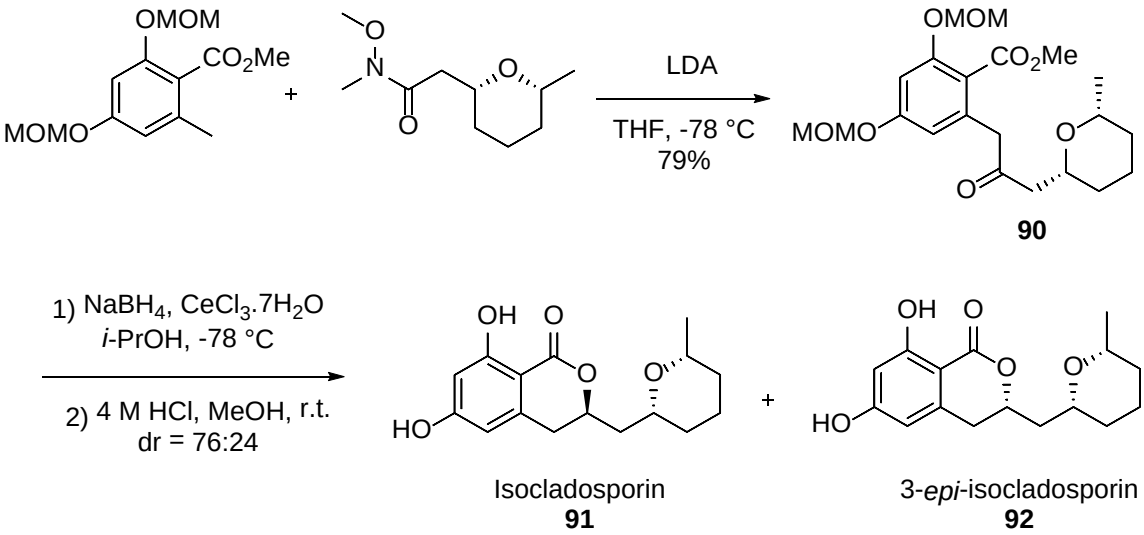


	A	B
With $CeCl_3$	97%	3%
Without $CeCl_3$	0%	100%

Scheme 1.52

The Luche procedure has been exploited in the total synthesis of isocladosporin **91** and 3-*epi*-isocladosporin **92**, as seen below in **Scheme 1.53**.[178] In this synthesis the authors used sodium borohydride and cerium trichloride at -78 °C to diastereoselectively reduce the ketone in **90** to afford the *in situ* lactone, and isocladosporin **91** and 3-*epi*-isocladosporin **92**. All other

reduction conditions resulted in loss of diastereoselectivity and/or deprotection of the methoxymethyl acetal (MOM) protecting groups.



Scheme 1.53

Samarium(II) iodide's role as a one-electron reducing agent has been recently reviewed.[179] Samarium(II) iodide may be used to reduce α-functionalized carbonyl compounds,[180] arenes,[181] ketones and aldehydes,[182] carboxylic acids,[183] organic halides[182] and nitro compounds.[184] The reactivity of SmI_2 is strongly dependent on the choice of reaction solvent. The use of hexamethylphosphoramide **93** (HMPA) as a co-solvent in samarium iodide reductions has been shown to allow the reductions to proceed under much milder conditions than in its absence.[185] More recently, hydroxylated HMPA[186] **94** and dipyrrolidinomethylaminophosphoric acid triamide (DPMPA)[187] **95** have also been reported as activators of samarium(II) iodide reductions (**Figure 1.9**).

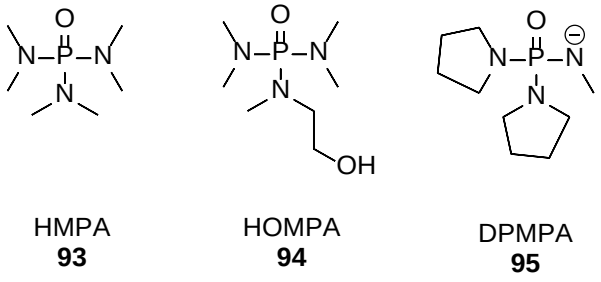
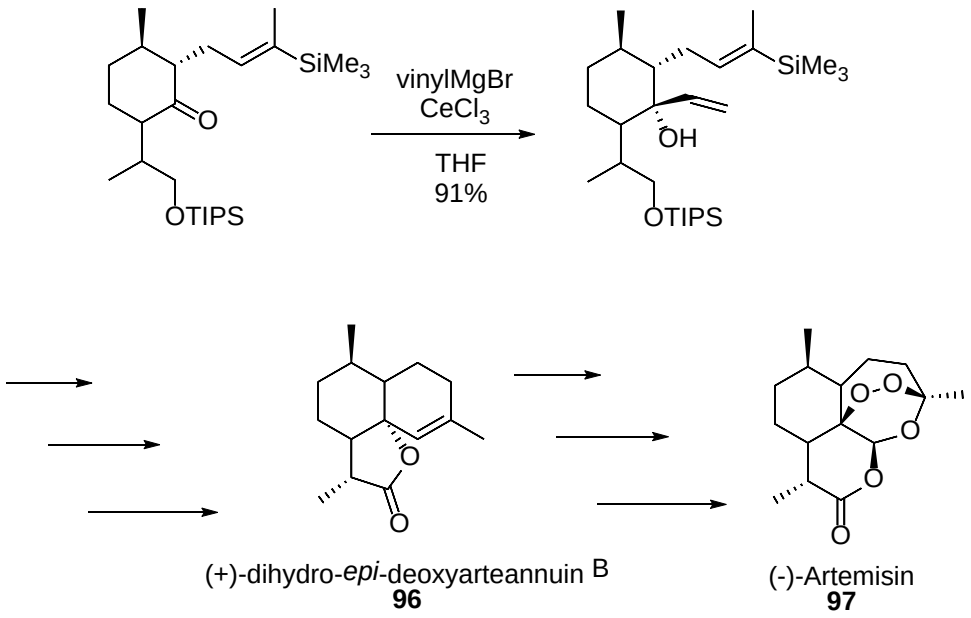


Figure 1.9

1.6.4 Carbon-carbon bond forming reactions using lanthanide catalysis

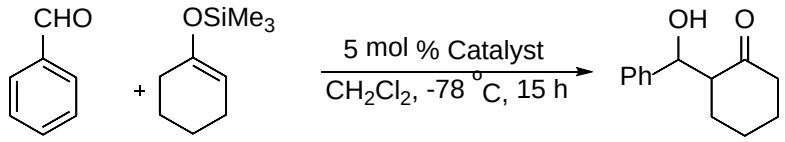
Lanthanide reagents have found many uses in carbon-carbon bond forming reactions. Organocerium reagents have proved to be very efficient alternatives to Grignard and organolithium reagents, and have been recently reviewed by Sambri.[188] Other organolanthanides have also been shown to be effective alternatives, but the low cost and proven success of organoceriums has led to their preferential use.

Organoceriums are prepared *in situ* by transmetalation reactions from organolithium or organomagnesium reagents.[189–193] The structure of the active species remains undetermined. These reagents have been used to react with aldehydes and ketones to give the corresponding alcohol, often in higher yields than those reported when using traditional reagents. This was exploited in a key step in the total synthesis of (+)-dihydro-epi-deoxyarteannuin B **96**, a key intermediate in the synthesis of (-)-Artemisin **97**, as shown in **Scheme 1.54**.[194]



Scheme 1.54

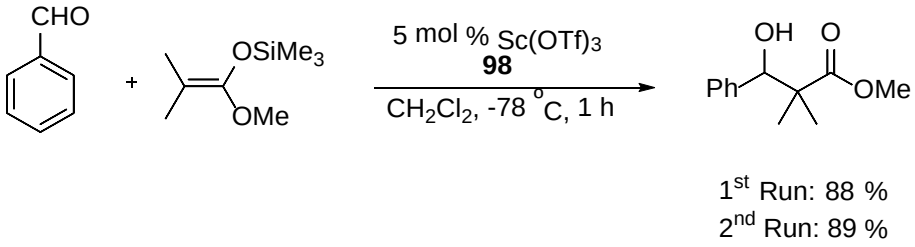
Scandium (III) triflate was found to be an effective catalyst for the aldol reaction of silyl enol ethers with aldehydes.[157,195] Kobayashi and co-workers examined the effect of typical lanthanide triflates in this reaction, and found $Sc(OTf)_3$ **98** to be more effective than either the ytterium or ytterbium triflates (**Scheme 1.55)**.[196]



Entry	Catalyst		Yield (%)
1	$Sc(OTf)_3$	**98**	81
2	$Y(OTf)_3$	**99**	Trace
3	$Yb(OTf)_3$	**100**	Trace

Scheme 1.55

Kobayashi and co-workers also investigated the recovery and re-use of the scandium triflate catalysts for these aldol reactions.[195] The scandium triflate **98** was recovered almost quantitatively after the reaction was complete. The recovered catalyst's activity was seemingly undiminished as it performed comparably in the subsequent run (**Scheme 1.56**).



Scheme 1.56

As scandium(III) triflate is more soluble in water than in organic solvents it can be recovered from the aqueous layer as shown in **Figure 1.10**.

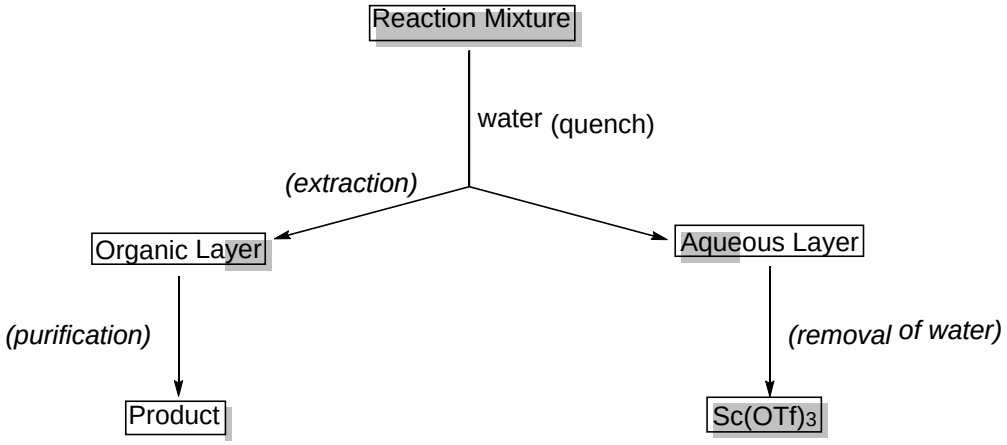
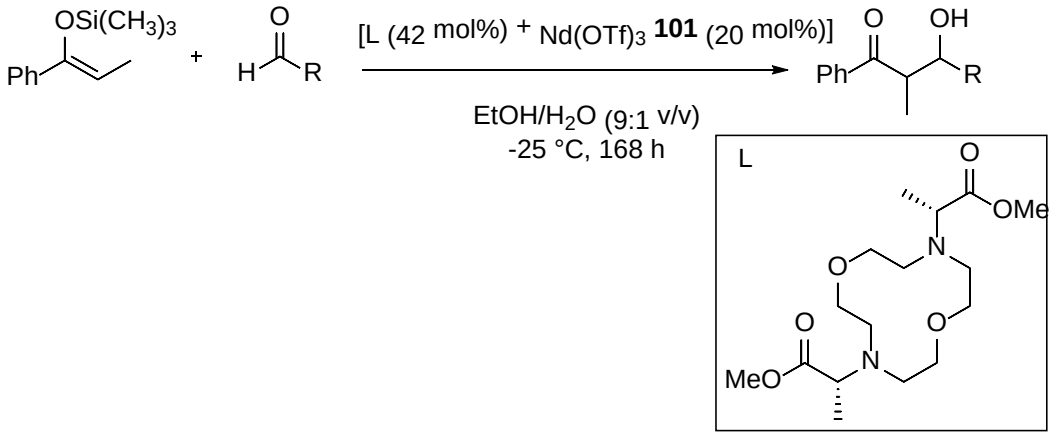


Figure 1.10

More recently, Allen *et al*. reported the development of chiral lanthanide-containing complexes that produce Mukaiyama aldol products with excellent enantioselectivities.[197] Mukaiyama aldol reactions are used to synthesise β-hydroxy carbonyls, and requires a catalyst to induce stereochemistry. When the pre-catalyst L shown in **Scheme 1.57** is used in conjunction with neodymium triflate **101** for aromatic aldehydes, excellent yields and good enantioselectivities were obtained. However when the same conditions were employed with alkyl aldehydes, the efficacy of the reaction significantly decreased.



Aldehyde	Yield	*syn:anti*
p-Chlorobenzaldehyde	93%	36:1
p-Methylbenzaldehyde	90%	12:1
Formaldehyde	56%	1:3

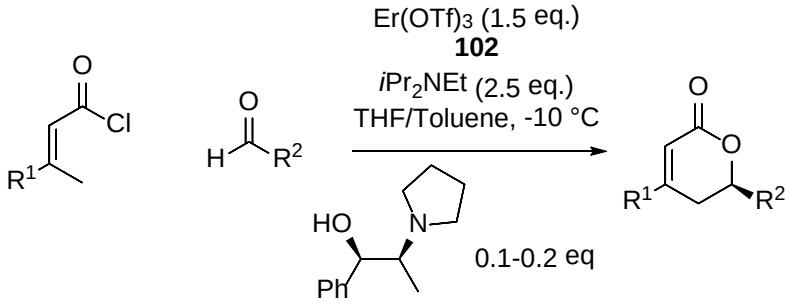
Scheme 1.57

1.6.5 Lanthanide triflates as Lewis acid catalysts

Kobayashi first reported the use of lanthanide triflates as water compatible Lewis acids.[198–200] Use of these lanthanide triflates as water compatible Lewis acids has several benefits.[201] These include the ability to use water as reaction solvent in place of organic solvent, and no necessity to use anhydrous solvents and substrates. In addition to this, aqueous solution allows for the use of the $Ln(OTf)_3$ hydrates, which are less costly than the anhydrous forms.[202]

The Diels-Alder reaction is a widely used synthetic transformation to yield cyclic compounds. These reactions are reversible, and are generally carried out at the lowest possible temperature. Lewis acid catalysts allow Diels-Alder reactions to proceed at room temperature or below, but can be accompanied by diene polymerization.[203]

Lanthanide triflates have been shown to successfully catalyse Diels-Alder reactions.[204] A recent example of this in the literature was reported by Tiseni when investigating tertiary-amine-catalyzed enantioselective [4+2] cycloadditions of α,β-unsaturated acid chlorides and the electron-poor aldehyde chloral.[205] The authors found the use of erbium triflate catalyst **102** improved the scope of the reactions considerably, allowing the use of a wide range of aromatic and aliphatic aldehydes. Some examples of the transformations achieved are shown in **Scheme 1.58**.



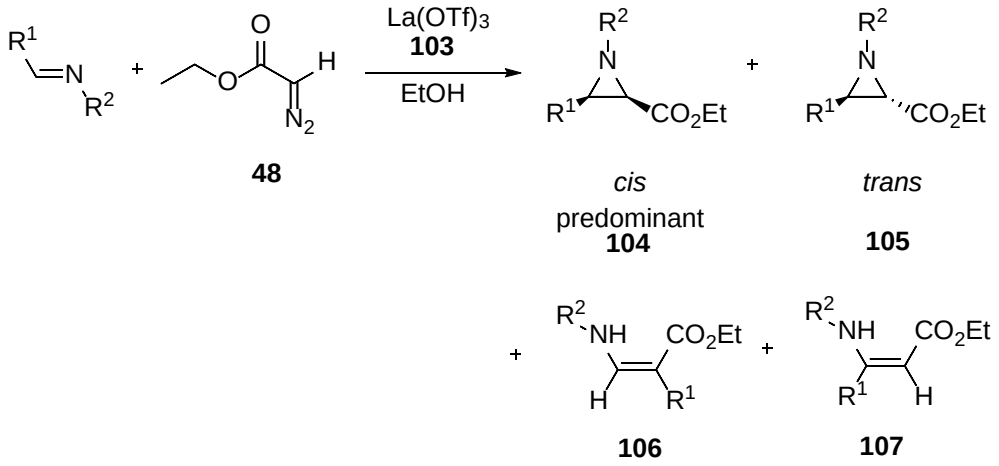
R^1	R^2	Yield [%]	*ee* [%]
Et	Ph	62	95
Ph	Ph	64	94
Ph	*m*-ClC_6H_4	78	93

Scheme 1.58

1.6.6 Lanthanides and diazo compounds

Aziridines are traditionally prepared using transition metal catalysis, either through addition of a nitrene moiety to an olefin, or the addition of a carbene moiety to an imine.[206–210] Wang and co-workers have reported lanthanide triflate catalysed aziridine synthesis from imines and diazo compounds.[211] This follows on from a publication by Templeton *et al*. of Lewis-acid catalysed synthesis of aziridines from ethyl diazoacetate **48** and imines.[212]

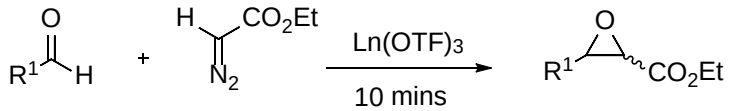
The authors used a variety of imines with ethyl diazoacetate **48** in the presence of 10 mol% of lanthanum triflate hydrate **103**. The reaction was found to proceed smoothly, even in protic solvents like ethanol. Ethanol was therefore used as the solvent of choice, as it allowed the use of the lanthanide triflates in their hydrated form, which are much less expensive than the anhydrous salts. Using these conditions, the reaction was found to be selective, affording predominately *cis* aziridines. A range of arylimines were reacted with ethyl diazoacetate **48** in ethanol to produce the corresponding aziridines as shown in **Scheme 1.59**.



Scheme 1.59

Wang and co-workers investigated a range of lanthanide triflate catalysts and loadings. It was found that a 10-15 mol % catalyst loading gave the optimum results, and that neodymium triflate **101** gave the highest yield and *cis* selectivities were obtained in all cases. The heavier lanthanides resulted in reduced selectivities.

Curini *et al*. reported the use of lanthanide triflates to form α,β-epoxy esters from the reaction of aldehydes with ethyl diazoacetate **48**, as illustrated in **Scheme 1.60**.[213] The authors tested a variety of reaction conditions but found that the best results were obtained in solvent-free conditions. A range of aliphatic and aromatic aldehydes were tested, and were found to be very reactive in all cases, with reactions times of only 10 minutes.



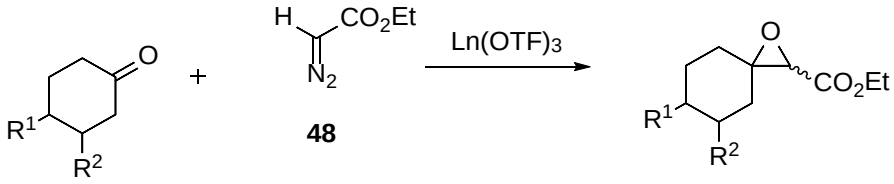
48

R^1	Ratio *cis*:*trans*	Yield with $La(OTf)_3$	Yield with $Eu(OTf)_3$	Yield with $Yb(OTf)_3$
CH_3	1:1	92%	35%	29%
C_5H_{11}	1:1	85%	41%	40%
C_6H_5	4:6	73%	19%	18%

Imine	R^1	R^2	Yield 104	Yield 105	Yield 106	Yield 107
1a	C_6H_5	C_6H_5	53%	-	13%	17%
1b	*p*-Cl-C_6H_4	C_6H_5	55%	-	-	-
1c	*p*-Me-C_6H_4	*p*-Cl-C_6H_4	57%	-	10%	13%

Scheme 1.60

The same reaction was attempted using ketones as substrates in an attempt to form glycidic esters. Ketones were found to be much less reactive than aldehydes, with no reaction occuring in several cases, and a significantly longer reaction time (72h) for those that did react (**Scheme 1.61**). It was determined that α-unsubstituted and α-monosubstituted cyclohexanones were the only substrates for which the process is effective.

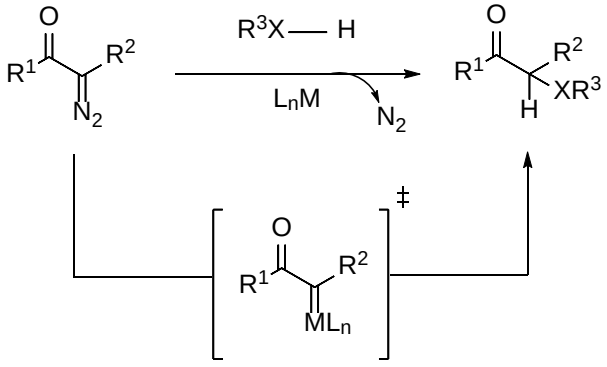


R^1	R^1	Yield with $La(OTf)_3$	Yield with $Eu(OTf)_3$	Yield with $Yb(OTf)_3$
H	H	87%	56%	46%
H	CH_3	83%	34%	32%
CH_3	H	81%	39%	34%

Scheme 1.61

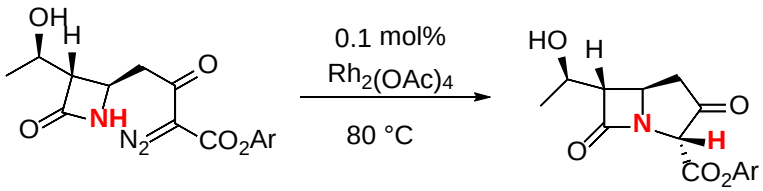
1.6.7 X-H insertion reactions

X-H insertion reactions of diazocarbonyl compounds have been comprehensively reviewed,[3,8,90,214,215] most recently by Gillingham[216] and McKervey.[4] X-H insertion is the insertion of a carbene into the X-H bond, as can be seen in **Scheme 1.62**.



Scheme 1.62

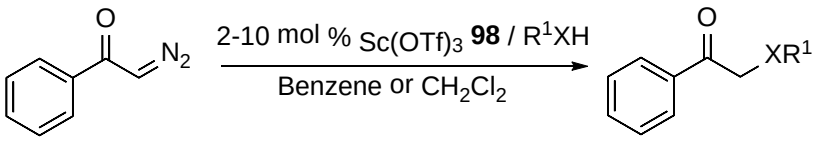
O-H, S-H and N-H insertion reactions have been the most studied reactions in this class. The most popular transition metal catalysts used in the literature to achieve these transformations have been rhodium(II) and copper(I). Rhodium(II) acetate catalysed X-H insertion has even been used commercially by Merck in the preparation of (+)-thienamycin **108**, a powerful antibiotic (**Scheme 1.63**).[217]



108

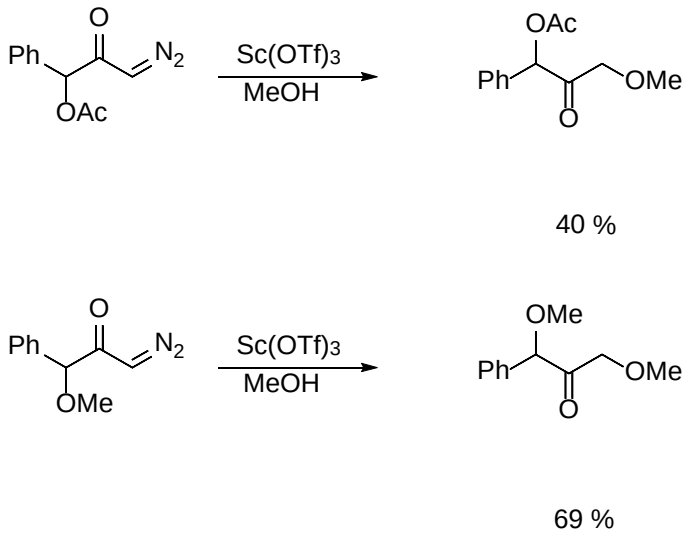
Scheme 1.63

To date there has been only one report in the literature using lanthanide catalysts to achieve X-H insertion from diazocarbonyl compounds. Pansare and co-workers[218] were looking for a route to α-alkoxy aryl ketones using mild conditions. They investigated a range of diazocarbonyl insertion reactions into the oxygen-hydrogen bonds in various alcohols, using scandium triflate **98** (2-10 mol%) as catalyst, and achieved successful O-H insertion (**Scheme 1.64**).



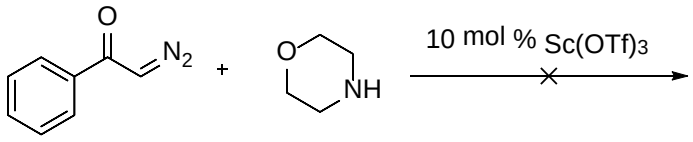
Scheme 1.64

The reactions were found to work well in either benzene or dichloromethane at room temperature, and was found to be faster for primary alcohols than secondary. Pansare also investigated O-H insertion using amino acid and hydroxy acid derived diazocarbonyl substrates. Diazoketone derived from *O*-acetyl mandelic acid were used as a substrate, and, underwent successful methanol insertion, showing the scope of the methodology (**Scheme 1.65**).



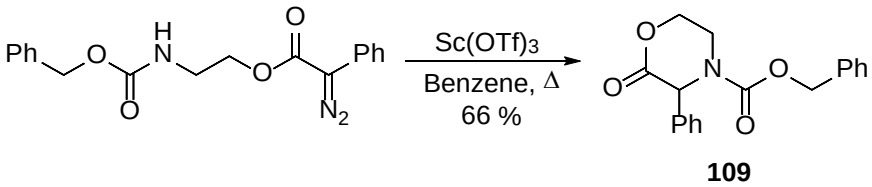
Scheme 1.65

The corresponding intermolecular N-H insertion reaction was also attempted with an amine, a carbamate and morpholine, but proved to be unsuccessful, as can be seen in **Scheme 1.66**.



Scheme 1.66

When the intramolecular reaction was attempted however, the reaction was successful yielding 3-phenyl-4-benzyloxycarbonyl morpholine-2-one **109** (**Scheme 1.67**).



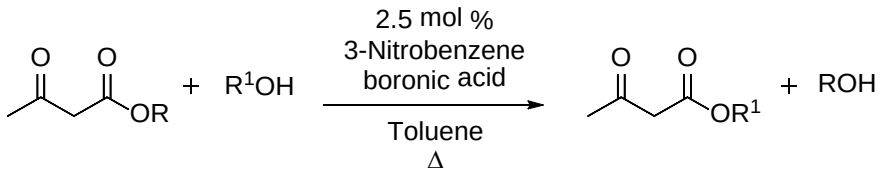
109

Scheme 1.67

1.7 Objectives of current research

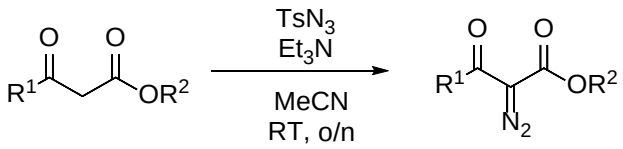
Following on from the above literature review, the objectives of this project are as follows:

- To synthesise a range of β-ketoesters with varying ester side-chains by transesterification of the corresponding alcohol, as shown in **Scheme 1.68**.



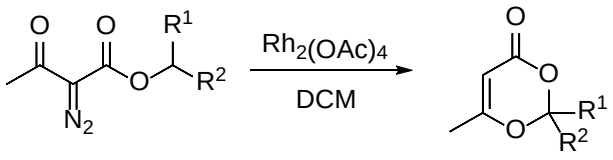
Scheme 1.68

- To prepare a range of novel α-diazo-β-ketoesters from β-ketoesters *via* diazo transfer (**Scheme 1.69**).



Scheme 1.69

- To examine the effect of varying different parameters of the diazo transfer reaction on the efficacy of the reaction in an attempt to make it more environmentally benign by employing some of the 12 Principles of Green Chemistry,[56] and more appealing to industry.
- To apply this improved methodology to continuous processing.
- To synthesise a range of dioxinones *via* rhodium(II) catalysed decomposition of α-diazo-β-ketoesters.



Scheme 1.70

- To investigate lanthanide catalysed decomposition reactions of α-diazo-β-ketoesters.

1.8 References

[1] R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert, P. Teyssie, *Tetrahedron Lett.* **1973**, 2233–2236.

[2] A. J. Hubert, A. F. Noels, A. J. Anciaux, P. Teyssie, *Synthesis* **1976**, 600–602.

[3] M. P. Doyle, *Chem. Rev.***1986**, *86*, 919–940.

[4] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981–10080.

[5] G. Maas, *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 8186–95.

[6] A. Padwa, D. J. Austin, *Angew. Chemie* **1994**, *106*, 1881–1899.

[7] M. Regitz, G. Maas, *Diazo Compounds. Properties and Synthesis.*, Academic, **1986**.

[8] T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160.

[9] Z. Zhang, J. Wang, *Tetrahedron* **2008,** *64***,** 6577-6605.

[10] F. W. Bollinger, L. D. Tuma, *Synlett* **1996**, 407–413.

[11] G. G. Hazen, L. M. Weinstock, R. Connell, F. W. Bollinger, *Synth. Commun.* **1981**, *11*, 947–956.

[12] C. C. Nawrat, C. J. Moody, *Nat. Prod. Rep.* **2011**, *28*, 1426–1444.

[13] C. C. Stock, H. C. Reilly, S. M. Buckley, D. A. Clarke, C. P. Rhoads, *Nature* **1954**, *173*, 71–72.

[14] J. Ehrlich, L. E. Anderson, G. L. Coffey, A. B. Hillegas, M. P. Knudsen, H. J. Koepsell, D. L. Kohberger, J. E. Oyaas, *Nature* **1954**, *173*, 72.

[15] Q. R. Bartzi, C. C. Elder, R. P. Frohardt, S. A. Fusari, T. H. Haskell, D. W. Johannessen, A. Ryder, *Nature* **1954**, *173*, 72–73.

[16] X. Lei, J. A. Porco Jr., *J. Am. Chem. Soc.* **2006**, *128*, 14790–14791.

[17] T. Kumamoto, Y. Kitani, H. Tsuchiya, K. Yamaguchi, H. Seki, T. Ishikawa, *Tetrahedron* **2007**, *63*, 5189–5199.

[18] K. C. Nicolaou, H. Li, A. L. Nold, D. Pappo, A. Lenzen, *J. Am. Chem. Soc.* **2007**, *129*, 10356–10357.

[19] T. Curtius, *Berichte der Dtsch. Chem. Gesellschaft* **1884**, *16*, 2230–2231.

[20] T. J. Curtius, *J. Prakt. Chem.* **1888**, *38*, 396–440.

[21] F. Arndt, J. Amende, *Berichte der Dtsch. Chem. Gesellschaft* **1928**, *61B*, 1122–1124.

[22] F. Arndt, B. Eistert, *Berichte der Dtsch. Chem. Gesellschaft* **1928**, *61B*, 1118–1122.

[23] F. Arndt, B. Eistert, W. Partale, *Berichte der Dtsch. Chem. Gesellschaft* **1927**, *60B*, 1364–1370.

[24] F. Arndt, B. Eistert, W. Partale, *Berichte der Dtsch. Chem. Gesellschaft* **1928**, *61B*, 1107–1118.

[25] W. Bradley, R. Robinson, *J. Am. Chem. Soc.* **1930**, *52*, 1558–1565.

[26] M. Regitz, *Angew. Chemie, Int. Ed. English* **1967**, *6*, 733–749.

[27] M. Regitz, *Synthesis* **1972**, 351–373.

[28] M. Regitz, F. Menz, *Chem. Ber.* **1968**, *101*, 2622–2632.

[29] G. Regitz, M.; Maas, *Diazo Compounds: Properties and Synthesis, Academic Press, Orlando*, **1986**.

[30] J. B. Hendrickson, W. A. Wolf, *J. Org. Chem.* **1968**, *33*, 3610–3618.

[31] R. L. Danheiser, R. F. Miller, R. G. Brisbois, *Org. Synth.* **1996**, *73*, 134–143.

[32] R. L. Danheiser, R. F. Miller, R. G. Brisbois, S. Z. Park, *J. Org. Chem.* **1990**, *55*, 1959–1964.

[33] D. F. Taber, R. B. Sheth, P. V Joshi, *J. Org. Chem.* **2005**, *70*, 2851–2854.

[34] M. K. Muthyala, S. Choudhary, A. Kumar, *J. Org. Chem.* **2012**, *77*, 8787–8791.

[35] A. M. Harned, W. M. Sherrill, D. L. Flynn, P. R. Hanson, *Tetrahedron* **2005**, *61*, 12093–12099.

[36] G. M. Green, N. P. Peet, W. A. Metz, *J. Org. Chem.* **2001**, *66*, 2509–2511.

[37] A. M. P. Koskinen, L. Munoz, *J. Chem. Soc. Chem. Commun.* **1990**, 652–653.

[38] M. Presset, D. Mailhol, Y. Coquerel, J. Rodriguez, *Synthesis* **2011**, 2549–2552.

[39] M. Regitz, in *Newer Methods Prep. Org. Chem* **1971**, pp. 81–126.

[40] G. G. Hazen, F. W. Bollinger, F. E. Roberts, W. K. Russ, J. J. Seman, S. Staskiewicz, *Org. Synth.* **1996**, *73*, 144–151.

[41] A. B. Khare, C. E. McKenna, *Synthesis* **1991**, 405–406.

[42] H. M. L. Davies, W. R. Cantrell Jr., K. R. Romines, J. S. Baum, *Org. Synth.* **1992**, *70*, 93–100.

[43] C. E. Hatch III, J. S. Baum, T. Takashima, K. Kondo, *J. Org. Chem.* **1980**, *45*, 3281–3285.

[44] T. J. Curphey, *Org. Prep. Proced. Int.* **1981**, *13*, 112–115.

[45] L. D. Tuma, *Thermochim. Acta* **1994**, *243*, 161–167.

[46] J. B. Hendrickson, W. A. Wolf, *J. Org. Chem.* **1968**, *33*, 3610–3618.

[47] E. D. Goddard-Borger, R. V Stick, *Org. Lett.* **2007**, *9*, 3797–3800.

[48] P. T. Nyffeler, C.-H. Liang, K. M. Koeller, C.-H. Wong, *J. Am. Chem. Soc.* **2002**, *124*, 10773–10778.

[49] H. Ye, R. Liu, D. Li, Y. Liu, H. Yuan, W. Guo, L. Zhou, X. Cao, H. Tian, J. Shen, et al., *Org. Lett.* **2013**, *15*, 18–21.

[50] A. R. Katritzky, M. El Khatib, O. Bol'shakov, L. Khelashvili, P. J. Steel, *J. Org. Chem*. **2010,** *75***,** 6532-6539.

[51] G. Laus, V. Adamer, M. Hummel, V. Kahlenberg, K. Wurst, S. Nerdinger, H. Schottenberger, *Crystals* **2012**, *2*, 118–126.

[52] N. Fischer, E. D. Goddard-Borger, R. Greiner, T. M. Klapoetke, B. W. Skelton, J. Stierstorfer, *J. Org. Chem.* **2012**, *77*, 1760–1764.

[53] N. M. Smith, M. J. Greaves, R. Jewell, M. W. D. Perry, M. J. Stocks, J. P. Stonehouse, *Synlett* **2009**, 1391–1394.

[54] M. M. E. Delville, P. J. Nieuwland, P. Janssen, K. Koch, J. C. M. van Hest, F. P. J. T. Rutjes, *Chem. Eng. J.* **2011**, *167*, 556–559.

[55] D. B. Ramachary, V. V Narayana, K. Ramakumar, *Tetrahedron Lett.* **2008**, *49*, 2704–2709.

[56] J. C. Anastas, P. T.; Warner, in *Green Chem. Theory Pract.*, Oxford University Press, **1998**.

[57] S. Kobayashi, Editor, *Science of Synthesis: Water in Organic Synthesis.*, Georg Thieme Verlag, Stuttgart, Germany, **2012**.

[58] C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165.

[59] C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82.

[60] U. M. Lindstroem, *Chem. Rev.* **2002**, *102*, 2751–2771.

[61] M.-O. Simon, C.-J. Li, in *Green Tech. Org. Synth. Med. Chem.*, John Wiley & Sons Ltd., **2012**, pp. 263–295.

[62] M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415–1427.

[63] W. Wei, C. C. K. Keh, C.-J. Li, R. S. Varma, *Clean Technol. Environ. Policy* **2005**, *7*, 62–69.

[64] D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.

[65] R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159–164.

[66] D. Chandler, *Nature* **2005**, *437*, 640–647.

[67] R. Portmann, *PCT Int. Appl.* **1998,** WO9802423A1.

[68] J. J. Gajewski, *Acc. Chem. Res.* **1997**, *30*, 219–225.

[69] F. Fringuelli, O. Piermatti, F. Pizzo, in *Org. Synth. Water*, Blackie, **1998**, pp. 223–249.

[70] W. Lu, T. H. Chan, *J. Org. Chem.* **2001**, *66*, 3467–3473.

[71] T.-P. Loh, J.-R. Zhou, *Tetrahedron Lett.* **1999**, *40*, 9115–9118.

[72] C.-J. Li, T.-H. Chan, *Tetrahedron* **1999**, *55*, 11149–11176.

[73] S. F. M. van Dongen, R. L. M. Teeuwen, M. Nallani, S. S. van Berkel, J. J. L. M. Cornelissen, R. J. M. Nolte, J. C. M. van Hest, *Bioconjug. Chem.* **2009**, *20*, 20–23.

[74] B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chemie, Int. Ed.* **2015**, *54*, 6688–6728.

[75] B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. - A Eur. J.* **2015**, *21*, 2298–2308.

[76] S. T. R. Mueller, T. Wirth, *ChemSusChem* **2015**, *8*, 245–250.

[77] I. R. Baxendale, L. Brocken, C. J. Mallia, *Green Process. Synth.* **2013**, *2*, 211–230.

[78] T. N. Glasnov, C. O. Kappe, *Chem. - A Eur. J.* **2011**, *17*, 11956–11968.

[79] R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chemie, Int. Ed.* **2011**, *50*, 7502–7519.

[80] D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389.

[81] J. C. Pastre, D. L. Browne, S. V Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849–8869.

[82] D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680.

[83] J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57.

[84] S. V Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chemie, Int. Ed.* **2015**, *54*, 10122–10136.

[85] V. Hessel, *Chem. Eng. Technol.* **2009**, *32*, 1655–1681.

[86] A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chemie, Int. Ed.* **2009**, *48*, 8547–8550.

[87] R. A. Maurya, C. P. Park, J. H. Lee, D.-P. Kim, *Angew. Chemie, Int. Ed.* **2011**, *50*, 5952–5955.

[88] E. Rossi, P. Woehl, M. Maggini, *Org. Process Res. Dev.* **2012**, *16*, 1146–1149.

[89] M. Struempel, B. Ondruschka, R. Daute, A. Stark, *Green Chem.* **2008**, *10*, 41–43.

[90] W. F. Ferstl, M. S. Schwarzer, S. L. Loebbecke, *Chemie Ing. Tech.* **2004**, *76*, 1326–1327.

[91] T. G. Archibald, J. C. Barnard, H. F. Reese, *U.S. Patent* **1998** US5854405A.

[92] L. D. Proctor, A. J. Warr, *Org. Process Res. Dev.* **2002**, *6*, 884–892.

[93] M. M. E. Delville, J. C. M. van Hest, F. P. J. T. Rutjes, *Beilstein J. Org. Chem.* **2013**, *9*, 1813–1818.

[94] R. A. Maurya, K.-I. Min, D.-P. Kim, *Green Chem.* **2014**, *16*, 116–120.

[95] S. T. R. Muller, D. Smith, P. Hellier, T. Wirth, *Synlett* **2014**, *25*, 871–875.

[96] P. Poechlauer, S. Braune, B. Dielemans, B. Kaptein, R. Obermueller, M. Thathagar, *Chim. Oggi* **2012**, *30*, 51–54.

[97] V. D. Filimonov, M. Trusova, P. Postnikov, E. A. Krasnokutskaya, Y. M. Lee, H. Y. Hwang, H. Kim, K.-W. Chi, *Org. Lett.* **2008**, *10*, 3961–3964.

[98] F. Le Callonnec, E. Fouquet, F.-X. Felpin, *Org. Lett.* **2011**, *13*, 2646–2649.

[99] R. C. R. Wootton, R. Fortt, A. J. de Mello, *Lab Chip* **2002**, *2*, 5–7.

[100] R. Fortt, R. C. R. Wootton, A. J. de Mello, *Org. Process Res. Dev.* **2003**, *7*, 762–768.

[101] B. Ahmed-Omer, D. A. Barrow, T. Wirth, *Tetrahedron Lett.* **2009**, *50*, 3352–3355.

[102] B. Ahmed, D. Barrow, T. Wirth, *Adv. Synth. Catal.* **2006**, *348*, 1043–1048.

[103] Z. Yu, Y. Lv, C. Yu, W. Su, *Tetrahedron Lett.* **2013**, *54*, 1261–1263.

[104] Z. Yu, Y. Lv, C. Yu, *Org. Process Res. Dev.* **2012**, *16*, 1669–1672.

[105] L. Malet-Sanz, J. Madrzak, S. V Ley, I. R. Baxendale, *Org. Biomol. Chem.* **2010**, *8*, 5324–5332.

[106] H. Meerwein, G. Dittmar, R. Gollner, K. Hafner, F. Mensch, O. Steinfort, *Chem. Ber.* **1957**, *90*, 841–852.

[107] J. Jacq, P. Pasau, *Chem. - A Eur. J.* **2014**, *20*, 12223–12233.

[108] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *J. Org. Chem.* **2010**, *75*, 8674–8676.

[109] L. J. Martin, A. L. Marzinzik, S. V Ley, I. R. Baxendale, *Org. Lett.* **2011**, *13*, 320–323.

[110] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *Chem. - A Eur. J.* **2011**, *17*, 9586–9589.

[111] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *Tetrahedron* **2013**, *69*, 2276–2282.

[112] S. T. R. Muller, A. Murat, P. Hellier, T. Wirth, *Org. Process Res. Dev.* **2016**, *20*, 495–502.

[113] M. P. Doyle, in *Organomet. Chem. II Vol 12*, Pergamon Press, New York, **1995**.

[114] H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203–5223.

[115] E. Nakamura, N. Yoshikai, M. Yamanaka, *J. Am. Chem. Soc.* **2002**, *124*, 7181–7192.

[116] T. R. Felthouse, *Prog. Inorg. Chem.* **1982**, *29*, 73–166.

[117] E. B. Boyar, S. D. Robinson, *Coord. Chem. Rev.* **1983**, *50*, 109–208.

[118] L. Wolff, *Justus Liebigs Ann. Chem.* **1912**, *394*, 23–108.

[119] N. R. Candeias, A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, in *Compr. Org. Synth. (2nd Ed.)*, Elsevier B.V., **2014**, pp. 944–991.

[120] R. R. Kumar, M. Balasubramanian, in *Name React. Homol.*, John Wiley & Sons, Inc., **2009**, pp. 257–273.

[121] H. Meier, K. P. Zeller, *Angew. Chemie* **1975**, *87*, 52–63.

[122] L. L. Rodina, I. K. Korobitsyna, *Usp. Khim.* **1967**, *36*, 611–635.

[123] W. Kirmse, *European J. Org. Chem.* **2002**, 2193–2256.

[124] P. Visser, R. Zuhse, M. W. Wong, C. Wentrup, *J. Am. Chem. Soc.* **1996**, *118*, 12598–12602.

[125] G. Burdzinski, Y. Zhang, J. Wang, M. S. Platz, *J. Phys. Chem. A* **2010**, *114*, 13065–13068.

[126] G. Burdzinski, J. Rehault, J. Wang, M. S. Platz, *J. Phys. Chem. A* **2008**, *112*, 10108–10112.

[127] J. Wang, G. Burdzinski, J. Kubicki, T. L. Gustafson, M. S. Platz, *J. Am. Chem. Soc.* **2008**, *130*, 5418–5419.

[128] Y. Wang, T. Yuzawa, H. Hamaguchi, J. P. Toscano, *J. Am. Chem. Soc.* **1999**, *121*, 2875–2882.

[129] Y. Chiang, A. J. Kresge, V. V Popik, *J. Am. Chem. Soc.* **1999**, *121*, 5930–5932.

[130] F. Arndt, B. Eistert, *Berichte der Dtsch. Chem. Gesellschaft* **1935**, *68B*, 200–208.

[131] S. Zrig, B. Andrioletti, E. Rose, J. Colin, *Tetrahedron Lett.* **2005**, *46*, 1103–1105.

[132] C. Thommen, C. K. Jana, M. Neuburger, K. Gademann, *Org. Lett.* **2013**, *15*, 1390–1393.

[133] C. N. Slattery, A. Ford, A. R. Maguire, *Tetrahedron* **2010**, *66*, 6681–6705.

[134] M. P. Doyle, M. Ratnikov, Y. Liu, *Org. Biomol. Chem.* **2011**, *9*, 4007–4016.

[135] H. Meerwein, H. Rathjen, H. Werner, *Berichte der Dtsch. Chem. Gesellschaft* **1942**, *75B*, 1610–1622.

[136] F. Greuter, J. Kalvoda, O. Jeger, *Proc. Chem. Soc. London* **1958**, 349.

[137] A. Demonceau, A. F. Noels, A. J. Hubert, P. Teyssie, *J. Chem. Soc. Chem. Commun.* **1981**, 688–689.

[138] J. D. White, P. Hrnciar, F. Stappenbeck, *J. Org. Chem.* **1997**, *62*, 5250–5251.

[139] M. G. Lloyd, M. D'Acunto, R. J. K. Taylor, W. P. Unsworth, *Org. Biomol. Chem.* **2016**, *14*, 1641–1645.

[140] N. T. M. Wilsmore, *J. Chem. Soc. Trans.* **1907**, *91*, 1938–1941.

[141] M. F. Carroll, A. R. Bader, *J. Am. Chem. Soc.* **1952**, *74*, 6305.

[142] M. F. Carroll, A. R. Bader, *J. Am. Chem. Soc.* **1953**, *75*, 5400–5402.

[143] A. R. Bader, H. S. Gutowsky, J. P. Heeschen, *J. Org. Chem.* **1956**, *21*, 821–822.

[144] C. Kaneko, M. Sato, J. Sakaki, Y. Abe, *J. Heterocycl. Chem.* **1990**, *27*, 25–30.

[145] M. Sato, K. Iwamoto, *Yuki Gosei Kagaku Kyokaishi* **1999**, *57*, 76–83.

[146] R. H. Tale, R. N. Adude, *Tetrahedron Lett.* **2006**, *47*, 7263–7265.

[147] D. D. Nekrasov, *Chem. Heterocycl. Compd.* **2001**, *37*, 925–938.

[148] M. Sato, *Yakugaku Zasshi* **1988**, *108*, 805–823.

[149] R. Cookson, T. N. Barrett, A. G. M. Barrett, *Acc. Chem. Res.* **2015**, *48*, 628–642.

[150] B. Kunze, F. Sasse, H. Wieczorek, M. Huss, *FEBS Lett.* **2007**, *581*, 3523–3527.

[151] K. A. Choquette, R. A. Flowers, in *Compr. Org. Synth. (2nd Ed.)*, Elsevier B.V., **2014**, pp. 278–343.

[152] T. Imamoto, *Kagaku, Zokan (Kyoto)* **1995**, *124*, 55–61.

[153] T. Imamoto, *Kidorui* **1995**, *27*, 79–95.

[154] H. B. Kagan, J. L. Namy, *Tetrahedron* **1986**, *42*, 6573–6614.

[155] H. B. Kagan, *Chem. Rev.* **2002**, *102*, 1805–1806.

[156] H. B. Kagan, M. Sasaki, J. Collin, *Pure Appl. Chem.* **1988**, *60*, 1725–1730.

[157] S. Kobayashi, *European J. Org. Chem.* **1999**, 15–27.

[158] S. Kobayashi, *Top. Organomet. Chem.* **1999**, *2*, 63–118.

[159] S. Kobayashi, in *Handb. Phys. Chem. Rare Earths*, Elsevier, **2000**, pp. 315–375.

[160] S. Kobayashi, in *Aqueous-Phase Organomet. Catal. (2nd Ed.)*, Wiley-VCH Verlag GmbH & Co. KGaA, **2004**, pp. 88–99.

[161] G. A. Molander, *Chem. Rev.* **1992**, *92*, 29–68.

[162] G. A. Molander, in *Chem. Met.-Carbon Bond*, Wiley, **1989**, pp. 319–396.

[163] P. G. Steel, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2727–2751.

[164] T.-L. Ho, *Synthesis* **1973**, 347–354.

[165] A. C. Apolinario, A. M. T. Silva, B. F. Machado, H. T. Gomes, P. P. Araujo, J. L. Figueiredo, J. L. Faria, *Appl. Catal. B Environ.* **2008**, *84*, 75–86.

[166] B. Saha, S. Deka, D. Gupta, K. J. Deori, Indian Patent. Appl., **2014,** IN2013DE01346A.

[167] M. Paul, S. Shirase, Y. Morimoto, L. Mathey, M. Balasubramanian, S. Tanaka, S. Itoh, H. Tsurugi, K. Mashima, *Chem. - A Eur. J.* **2016**, *22*, 3897.

[168] L. Yu, F. Chen, W. Ji, C. Yang, *Faming Zhuanli Shenqing*, **2015,** CN105152829A.

[169] M.-Y. Chang, C.-Y. Tsai, *Tetrahedron Lett.* **2014**, *55*, 5548–5550.

[170] F. Khan, U. Kushwaha, *Res. J. Pharm. Biol. Chem. Sci.* **2013**, *4*, 444–457.

[171] F. Khan, U. Kushwaha, A. K. Singh, *J. Chem. Pharm. Res.* **2012**, *4*, 3715–3726.

[172] T. Ogata, Y. Sugiyama, S. Ito, K. Nakano, E. Torii, A. Nishiuchi, T. Kimachi, *Tetrahedron* **2013**, *69*, 10470–10476.

[173] K.-I. Hayashi, F.-R. Chang, Y. Nakanishi, K. F. Bastow, G. Cragg, A. T. McPhail, H. Nozaki, K.-H. Lee, *J. Nat. Prod.* **2004**, *67*, 990–993.

[174] J. D. White, G. L. Larson, *J. Org. Chem.* **1978**, *43*, 4555–4556.

[175] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

[176] J. L. Luche, L. Rodriguez-Hahn, P. Crabbe, *J. Chem. Soc. Chem. Commun.* **1978**, 601–602.

[177] A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

[178] D. K. Mohapatra, S. Maity, S. Banoth, R. G. Gonnade, J. S. Yadav, *Tetrahedron Lett.* **2016**, *57*, 53–55.

[179] M. Szostak, M. Spain, D. J. Procter, *Chem. Soc. Rev.* **2013**, *42*, 9155–9183.

[180] M. Szostak, M. Spain, D. J. Procter, *Chem. - A Eur. J.* **2014**, *20*, 4222–4226.

[181] T. V Chciuk, R. A. Flowers, *J. Am. Chem. Soc.* **2015**, *137*, 11526–11531.

[182] S. Maity, S. Hoz, *Chem. - A Eur. J.* **2015**, *21*, 18394–18400.

[183] M. Szostak, M. Spain, D. J. Procter, *Org. Lett.* **2014**, *16*, 5052–5055.

[184] J. A. Ferreira Ramos, C. S. Araujo, T. J. Nagem, J. G. Taylor, *J. Heterocycl. Chem.* **2015**, *52*, 54–58.

[185] J. Inanaga, M. Ishikawa, M. Yamaguchi, *Chem. Lett.* **1987**, 1485–1486.

[186] S. Halder, S. Hoz, *J. Org. Chem.* **2014**, *79*, 2682–2687.

[187] C. E. McDonald, J. R. Ramsey, D. G. Sampsell, L. A. Anderson, J. E. Krebs, S. N. Smith, *Tetrahedron* **2013**, *69*, 2947–2953.

[188] E. Marcantoni, L. Sambri, in *Compr. Org. Synth. (2nd Ed.)*, Elsevier B.V., **2014**, pp. 267–277.

[189] T. Imamoto, T. Kusumoto, M. Yokoyama, *J. Chem. Soc. Chem. Commun.* **1982**, 1042–1044.

[190] T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, M. Yokoyama, *J. Org. Chem.* **1984**, *49*, 3904–3912.

[191] T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233–4236.

[192] T. Imamoto, Y. Sugiura, *J. Organomet. Chem.* **1985**, *285*, C21–C23.

[193] T. Imamoto, N. Takiyama, K. Nakamura, *Tetrahedron Lett.* **1985**, *26*, 4763–4766.

[194] G. B. Dudley, D. A. Engel, I. Ghiviriga, H. Lam, K. W. C. Poon, J. A. Singletary, *Org. Lett.* **2007**, *9*, 2839–2842.

[195] S. Kobayashi, I. Hachiya, H. Ishitani, M. Araki, *Synlett* **1993**, 472–474.

[196] S. Kobayashi, *Synlett* **1994**, 689–701.

[197] Y. Mei, P. Dissanayake, M. J. Allen, *J. Am. Chem. Soc.* **2010**, *132*, 12871–12873.

[198] S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209–217.

[199] S. Kobayashi, *European J. Org. Chem.* **1999**, 15–27.

[200] S. Kobayashi, *Chem. Lett.* **1991**, 2187–2190.

[201] S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209–217.

[202] W. Xie, J. Fang, J. Li, P. G. Wang, *Tetrahedron* **1999**, *55*, 12929–12938.

[203] P. Yates, P. Eaton, *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437.

[204] S. Kobayashi, I. Hachiya, M. Araki, H. Ishitani, *Tetrahedron Lett.* **1993**, *34*, 3755–3758.

[205] P. S. Tiseni, R. Peters, *Chem. - A Eur. J.* **2010**, *16*, 2503–2517.

[206] D. A. Evans, M. T. Bilodeau, M. M. Faul, *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753.

[207] D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329.

[208] Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993**, *115*, 5326–5327.

[209] Z. Li, R. W. Quan, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5889–5890.

[210] J. M. Mohan, B. S. Uphade, V. R. Choudhary, T. Ravindranathan, A. Sudalai, *Chem. Commun.* **1997**, 1429–1430.

[211] W. Xie, J. Fang, J. Li, P. G. Wang, *Tetrahedron* **1999**, *55*, 12929–12938.

[212] L. Casarrubios, J. A. Perez, M. Brookhart, J. L. Templeton, *J. Org. Chem.* **1996**, *61*, 8358–8359.

[213] M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, *European J. Org. Chem.* **2002**, 1562–1565.

[214] T. Doyle, M. P.; McKervey, M. A.; Ye, *Modern Catalytic Methods in Organic Synthesis with Diazo Compunds, from Cyclopropanes to Ylides*, John Wiley And Sons Inc.: New York, **1998**.

[215] Z. Zhang, J. Wang, *Tetrahedron* **2008,** *64*, 6577-6605.

[216] D. Gillingham, N. Fei, *Chem. Soc. Rev*. **2013**, *42*, 4918-4931.

[217] T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, F. A. Bouffard, *J. Am. Chem. Soc.* **1980**, *102*, 6161–6163.

[218] S. V Pansare, R. P. Jain, A. Bhattacharyya, *Tetrahedron Lett.* **1999**, *40*, 5255–5258.

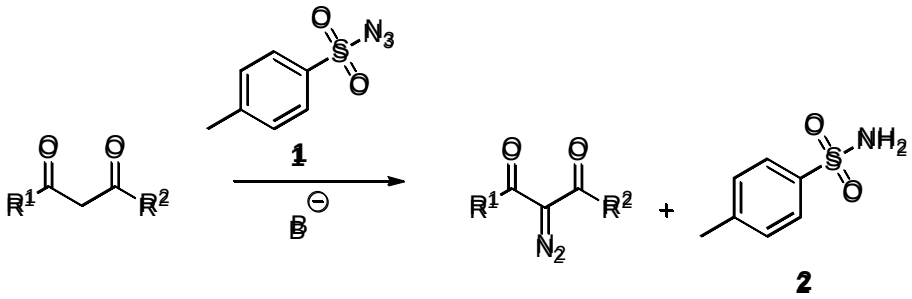
Chapter 2

Results and Discussion

Table of Contents

2.1 Introduction

α-Diazocarbonyl compounds play a key role in organic synthesis due to their ease of preparation and the range of chemical transformations which they can undergo, as previously discussed in Chapter 1. There are a number of methods of synthesising α-diazocarbonyl compounds, which are summarised in recent reviews,[1,2] however the most widely used method for the introduction of the diazo group to activated systems is by the diazo transfer reaction developed by Regitz (**Scheme 2.1**).[3–5]



Scheme 2.1

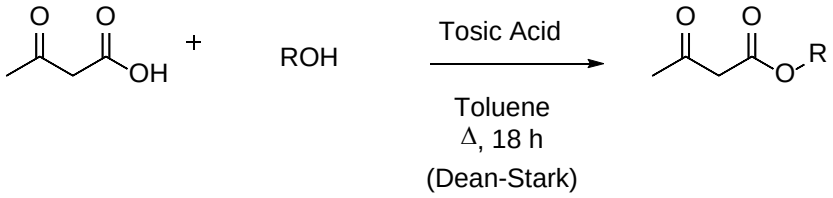
The Regitz methodology uses an aryl sulfonyl azide to transfer a diazo group to dicarbonyl compounds. The traditional diazo transfer reagents such as *p*-toluenesulfonyl azide **1** are inherently unstable, and have many risks associated with their use, as previously discussed in **Section 1.2.1**.[6,7] Therefore in recent years there has been a move towards developing alternative diazo transfer reagents that are safer to use without compromising on reaction efficacy.[8–12]

Anastas and Warner outlined their 12 Principles of Green Chemistry in 1998,[13] and since then the move towards green chemistry has received much attention. There is a call for pharmaceutical companies to develop processes that minimise the use and generation of hazardous substances, in an effort to reduce the environmental and health impacts of chemical production. This has led to a surge in research in both developing new 'green' processes, and redeveloping existing processes to be carried out in a manner that reduces their environmental impact. Previous work within this group has carried out initial studies using water as a solvent for diazo transfer with catalytic quantities of base.[14]

2.2 Synthesis of α-diazocarbonyl compounds

2.2.1 Preparation of ester derivatives

As the aim of this project is to examine the methodology associated with diazo transfer to β-ketoesters, it was necessary to prepare a range of novel α-diazo-β-ketoesters, as well as the corresponding non-commercially available β-ketoesters. Fischer esterification is one of the standard methods used for preparation of esters, as illustrated below in **Scheme 2.2**.[15,16]



Scheme 2.2

Previous work within the group attempted Fischer esterification as a means to prepare a range of structurally diverse β-ketoesters, some of which are shown below in **Figure 2.1**.

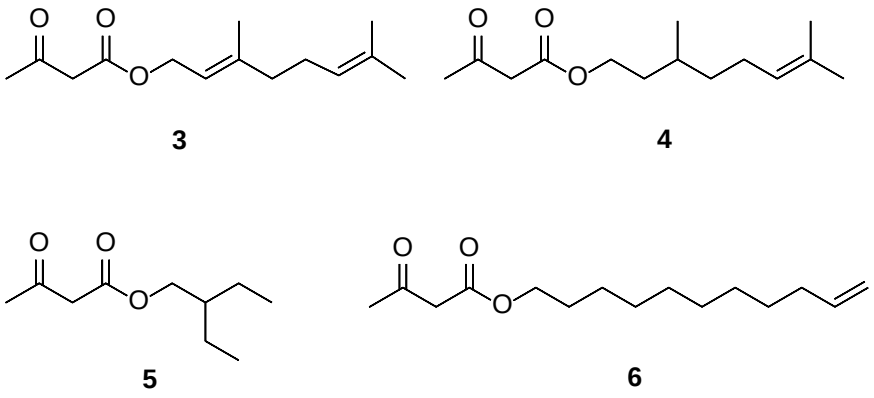
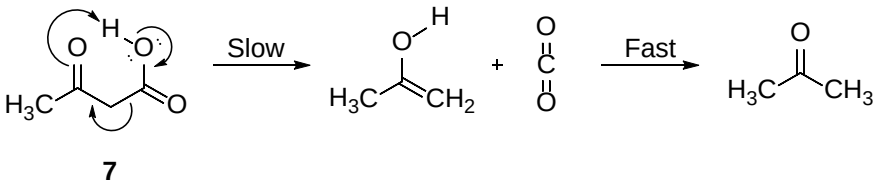


Figure 2.1 Long chain β-ketoesters to be synthesised.

However this method proved unsuccessful when used with the long chain alcohols required to synthesise the above β-ketoesters.[14] It is also thought that the particular carboxylic acid **7**

necessary for synthesis of the desired β-ketoesters is unstable under these conditions, thus preventing the desired reaction, as illustrated in **Scheme 2.3**.

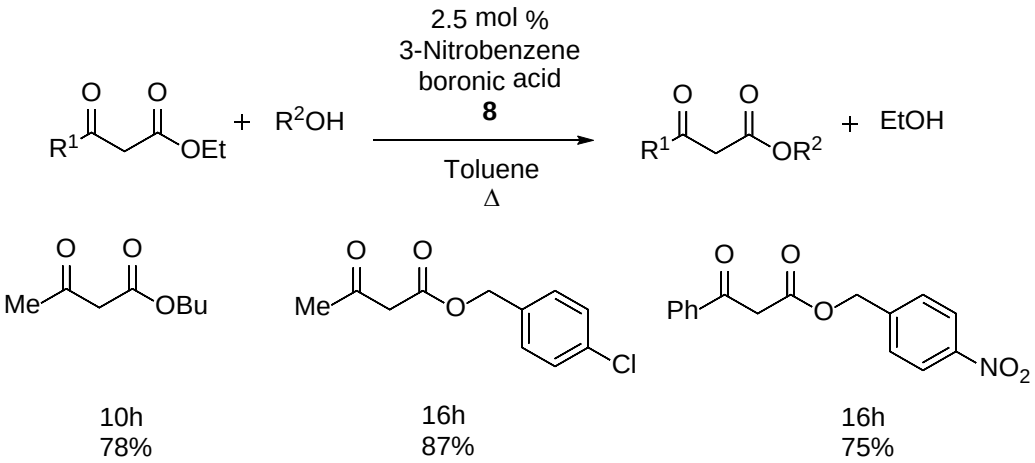


7

Scheme 2.3

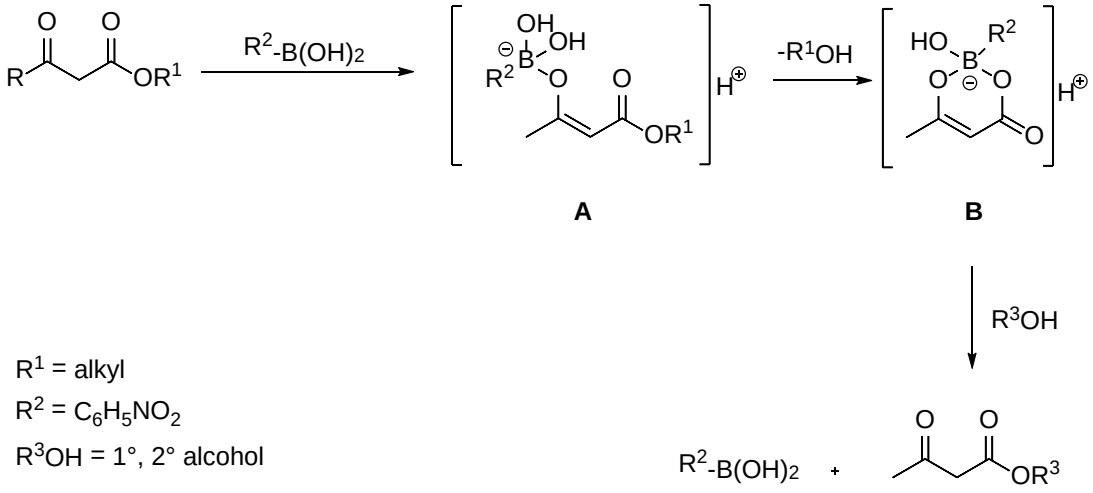
Tale and Adude reported the use of 3-nitrobenzeneboronic (3-NBBA) acid **8** as a catalyst for the transesterification of β-ketoesters with a wide range of alcohols.[17] The authors described this as an efficient, mild and environmentally benign protocol for the generation of a wide range of structurally diverse β-ketoesters in good to excellent yields, as shown below in **Scheme 2.4**.

The protocol involves heating the appropriate β-ketoester in the presence of the relevant alcohol and 2.5 mol% 3-NBBA **8** in toluene under reflux. A Dean-Stark apparatus is used to continuously remove the toluene-ethanol azeotrope.



Scheme 2.4

Kondaiah proposed a mechanism for the reaction as shown in **Scheme 2.5** below.[18] The proposed mechanism suggests that intermediate ***A*** is formed by boronic acid catalysed enolisation of the β-ketoester. The cyclic intermediate ***B*** is then formed by loss of R^1OH, and subsequent nucleophilic attack of the alcohol gives the desired ester product and efficiently regenerates the catalyst.

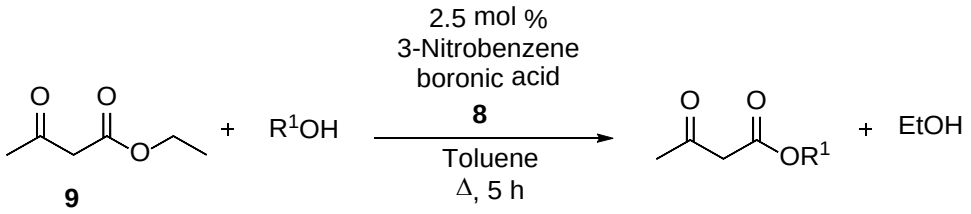


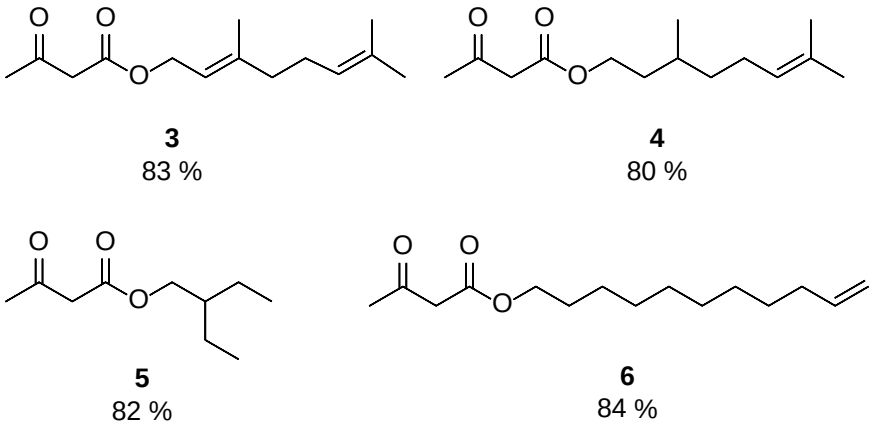
Scheme 2.5

Following a review of the literature four target non-commercially available esters were chosen for synthesis, which would give novel α-diazo-β-ketoesters products following diazo transfer. The first derivative chosen was generated using geraniol and ethyl acetoacetate **9** with 3-NBBA **8** in toluene. TLC analysis after 5 h indicated complete consumption of the ethyl acetoacetate **9**. The ^{1}H NMR spectrum of the crude reaction mixture showed evidence of the desired product **3** with a triplet at δ_H 5.35 ppm corresponding to the ester product, and approximately 5% of geraniol remaining was observed by a triplet at δ_H 5.41 ppm. Following column chromatography on silica gel using 90:10 hexane: ethyl acetate the product, 3,7-dimethyloct-6-enyl 3-oxobutanoate **3**, was obtained as a yellow oil in 83% yield (**Table 2.1**).

This method was widely used in the course of this project to generate a range of structurally diverse, non-commercially available esters. **Table 2.1** outlines the esters relevant to this section of the project; more derivatives will be discussed later.

Table 2.1 ***Summary of β-ketoesters synthesised by transesterification***

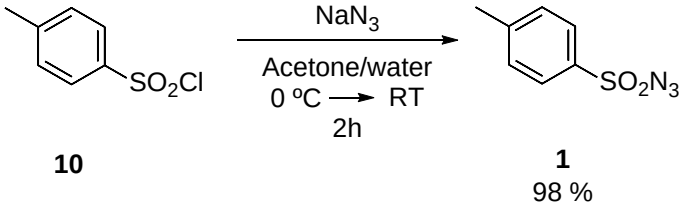




2.2.2 Preparation of tosyl azide 1

The most common method for the preparation of α-diazocarbonyl compounds is the Regitz methodology.[4,5] This method involves initial deprotonation of the α-hydrogen on the substrate by a base of sufficient strength, followed by transfer of a diazo group by a donor. These diazo transfer reagents are typically sulfonyl azides. Diazo transfer reagents have been extensively reviewed,[4,5,19,20] in particular the properties and hazards associated with them.[6,21]

p-Toluenesulfonyl (tosyl) azide **1** is the most commonly used diazo transfer regent, and was used as the diazo transfer regent of choice in the course of this project. Tosyl azide **1** was prepared from sodium azide and *p*-toluenesulfonyl chloride **10** according to a literature procedure by Curphey (**Scheme 2.6**).[22]

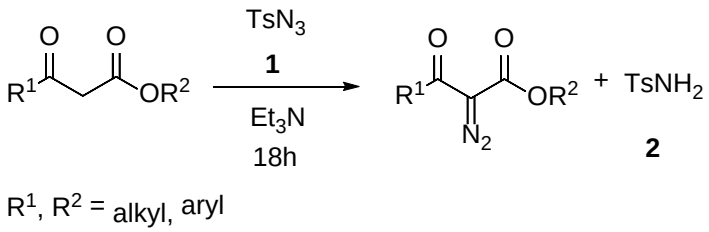


Scheme 2.6

Tosyl azide **1** is a heat and shock sensitive reagent, and so care is required when using this reagent. Once prepared, **1** is stored in a glass jar in the freezer, where it crystallises to a white solid. When needed, the jar is removed and warmed gently to room temperature. The reagent melts to clear oil. Precautions against the shock sensitive nature of the reagent include ensuring that any glass pipettes and vials being used are free of chips or cracks. Tosyl azide **1** was used without incident in the course of this research.

2.2.3 Diazo transfer reactions to β-ketoesters

The α-diazo-β-ketoesters prepared in this project were synthesised using a modified version of the Regitz methodology (**Scheme 2.7**). The traditional Regitz method involves dissolution of the substrate in acetonitrile, and addition of a suitable base (typically triethylamine) to the stirring solution. The diazo transfer reagent, usually *p*-toluenesulfonyl azide **1**, is then added dropwise to the reaction mixture at 0 °C, and the reaction mixture is allowed to warm to room temperature.



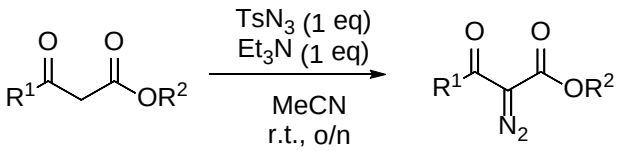
Scheme 2.7

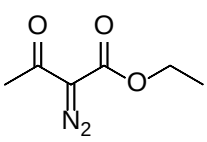
Previous work within our group found that this method gave long reaction times and low yields for β-ketoester substrates. The procedure was therefore modified with a room temperature addition of tosyl azide **1**. This was found to significantly increase the rate of reaction with a much more rapid initial appearance of the yellow colour associated with diazo transfer observed in the flask, as well as a slight exothermic reaction. It was found that this method resulted in shorter reaction times to approximately 80-90% conversion, with extra time required for reactions to go to completion. This procedural change allowed diazo transfer to proceed faster and in high yields, and was used in all cases in the course of this research.

Another modification was the use of a work-up involving a KOH wash, reported by Regitz.[23] This 9% potassium hydroxide wash was found to effectively remove the *p*-toluenesulfonyl amide **2** side product from the reaction mixture, and was used in the preparation of authentic samples of a range of α-diazo-β-ketoesters.

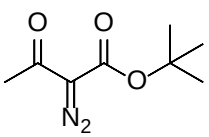
TLC analysis showed that typically after 18h, ethyl acetoacetate **9** was completely consumed. Ethyl 2-diazo-3-oxobutanoate **11** was obtained as a bright yellow oil in 90% yield. The ^{1}H NMR spectrum showed the product was pure and could be used without further purification. Using this procedure, we were able to prepare a range of α-diazo-β-ketoesters in high yields for this research. **Table 2.2** outlines the derivatives relevant to this portion of the project – further analogues will be discussed later.

Table 2.2 ***Summary of α–diazo-β-ketoesters***

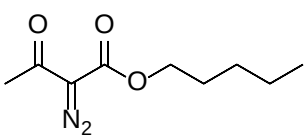




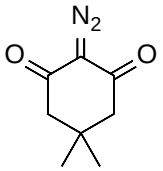
11
90 %



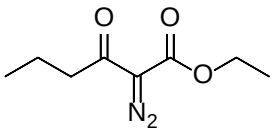
12
92 %



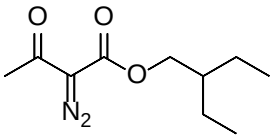
13
90 %



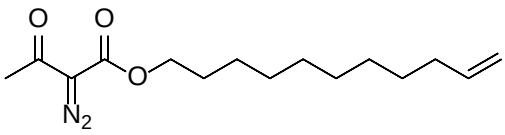
14
85 %



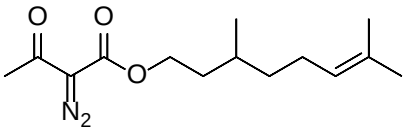
15
80 %



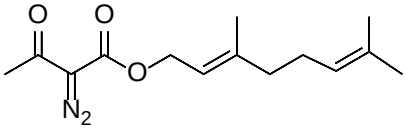
16
76 %



17
89 %



18
90 %



19
92 %

11-15 were synthesised from commercially available starting materials. **16-19** were prepared from β-ketoesters synthesised in **Section 2.2.1**. All samples were used without further purification.

One of the characteristic signals in the ^{1}H NMR spectra of these reaction mixtures is the disappearance of the 2H singlet in the region δ_H 3.44-3.46 ppm, corresponding to the α-protons in blue (**Figure 2.2**). The methyl group on the ketone also shifts from δ_H 2.24-2.28 ppm to δ_H 2.41-2.52 ppm when diazo transfer has taken place.

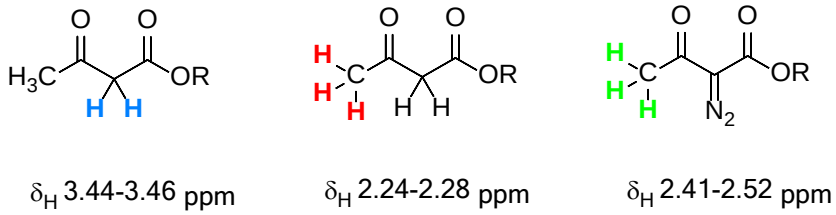


Figure 2.2 Key signal changes in the diazo transfer reaction for β-ketoesters.

In the ^{13}C NMR spectrum of the diazo product, the signal corresponding to the carbon of the ketone group is seen to shift from approximately δ_C 200 ppm to ~ δ_C 190 ppm. A peak for the quaternary carbon of the $C=N_2$ group would also be expected, however this is often not observed. In the cases of **11**, **14** and **16** above, this carbon was observed at δ_C 76.4, 83.6 and 75.8ppm respectively. In the IR spectra of these products, a new peak is seen in the region of 2130 cm^{-1}. This is lower than the expected region of $C=N_2$ group (2230-2300 cm^{-1}) due to the conjugation present in the molecule between the diazo group and the neighbouring carbonyl groups. This conjugation also results in a shift of the carbonyl absorptions from approximately 1710 cm^{-1} (ketone) and 1740 cm^{-1} (ester) in the starting material, to approximately 1660 cm^{-1} (ketone) and 1720 cm^{-1} (ester) in the product.

2.3 Diazo transfer as a greener process

2.3.1 Background

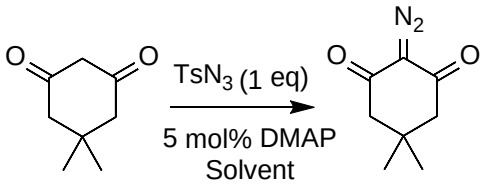
The aim of this section of the project is to revisit the synthesis and methodology used to generate α-diazo-β-ketoesters, because despite their versatility in organic synthesis and range of potential reaction pathways, diazo compounds are not widely used in large scale industrial processes. The key objectives of this study were to establish (1) the optimum solvent for diazo transfer to β-ketoesters, preferably a 'green' solvent; (2) the best base

loading, and choice of base for the diazo transfer reaction; and (3) if we could use the much safer polymer bound azide in combination with (1) and (2) to overcome the problem of removal of the *p*-toluenesulfonamide side-product from the reaction, leading to a potentially attractive process for use in industry.

2.3.2 Comparison of literature results

Ramachary and co-workers published a paper in which they carried out diazo transfer in ionic liquids with 5 mol% of base.[24] The authors reported high yields with short reaction times, in an unusual system where the ionic liquid acted as a base for the reaction. It was noted that a catalytic quantity of amine base served to accelerate the reaction rate. As a comparison, two entries were included in a table, reporting that diazo transfer to dimedone **20** was achieved in excellent yields in both acetonitrile and dichloromethane in only one and two hours respectively, using 5 mol% DMAP. These results are reported below.

Table 2.3 ***Literature Results***[24]



20 **14**

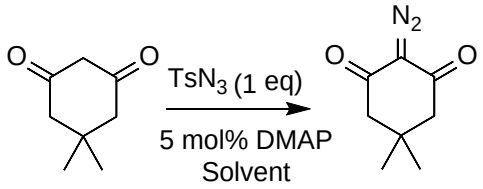
Substrate	*D.T. Reagent*	*Solvent*	*Reaction Time (h)*	*Yield*[1]
Dimedone	TsN_3	CH_3CN	1	94%
Dimedone	TsN_3	CH_2Cl_2	2	90%

[1] % Yields reported following column chromatography on silica gel.

These high yields in such a short reaction time were unprecedented from our review of the literature, and from the extensive diazo chemistry done in our group to date across a range

of diazo projects. Therefore it was decided to attempt to replicate these results, as shown below in **Table 2.4**.

Table 2.4 ***Attempts to replicate literature results***



20 **14**

Substrate	*D.T. Reagent*	*Solvent*	*Reaction Time (h)*	*Yield*[1]
Dimedone	TsN_3	CH_3CN	1	2.5%
Dimedone	TsN_3	CH_2Cl_2	2	8.4%

[1] % Yields reported following column chromatography on silica gel.

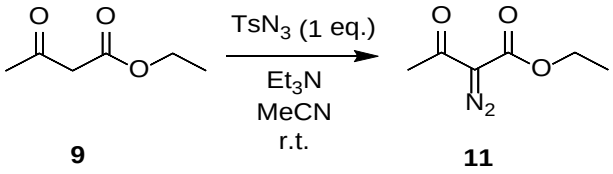
As can be seen above, the yields obtained are substantially lower than those reported by Ramachary and co-workers. It should be noted that conditions for chromatography were not reported in the paper, and so the solvent system that gave the best separation was chosen. Although we were unable to reproduce the results above, this is not unexpected from a comprehensive review of the literature, and from other experiments carried out in the course of this research, all of which indicate a longer reaction time is required to achieve a high yielding diazo transfer reaction.

2.3.3 Initial investigation into using sub-stoichiometric quantities of base

In order to investigate whether diazo transfer using sub-stoichiometric quantities of base was possible, a screen was carried out. Ethyl acetoacetate **9** was chosen as a model substrate because, in addition to the disappearance of the CH_2 singlet at δ_H 3.5 ppm, there is a clear shift of the CH_2 quartet of the ethyl side chain from δ_H 4.2 ppm in the ester, to δ_H 4.3 ppm in the corresponding α-diazo β-ketoester. The CH_3 of the methyl ketone is also seen to move from δ_H 2.3 ppm in the starting material, to δ_H 2.5ppm in the diazo product. Diazo transfer to

9 was attempted using 100 mol%, 50 mol%, 5 mol% and 1 mol% of triethylamine. Approximately 200 mg of **9** was used in 15 mL of acetonitrile. Reaction time was kept constant at 5 hours, in order to accurately compare conversions. The results are shown in **Table 2.5** below.

Table 2.5 ***Base loading screen***



9 **11**

Entry	***Reaction Time***	***Et_3N Loading***	***Concentration***	***Conversion***
1	5h	100 mol%	0.10 mol/ L	100%
2	5h	50 mol%	0.11 mol/ L	100%
3	5h	5 mol%	0.11 mol/ L	100%
4	5h	1 mol%	0.11 mol/ L	100%

The ^{1}H NMR spectra of the crude reaction mixtures showed no evidence of any starting ester, however the KOH wash had failed to fully remove the *p*-toluenesulfonamide **2** by-product. Despite this, we were initially very pleased with this result, as 100% diazo transfer in 5h had been achieved with only 1 mol% of base. However, when stacked as below in **Figure 2.2** a discrepancy can be seen.

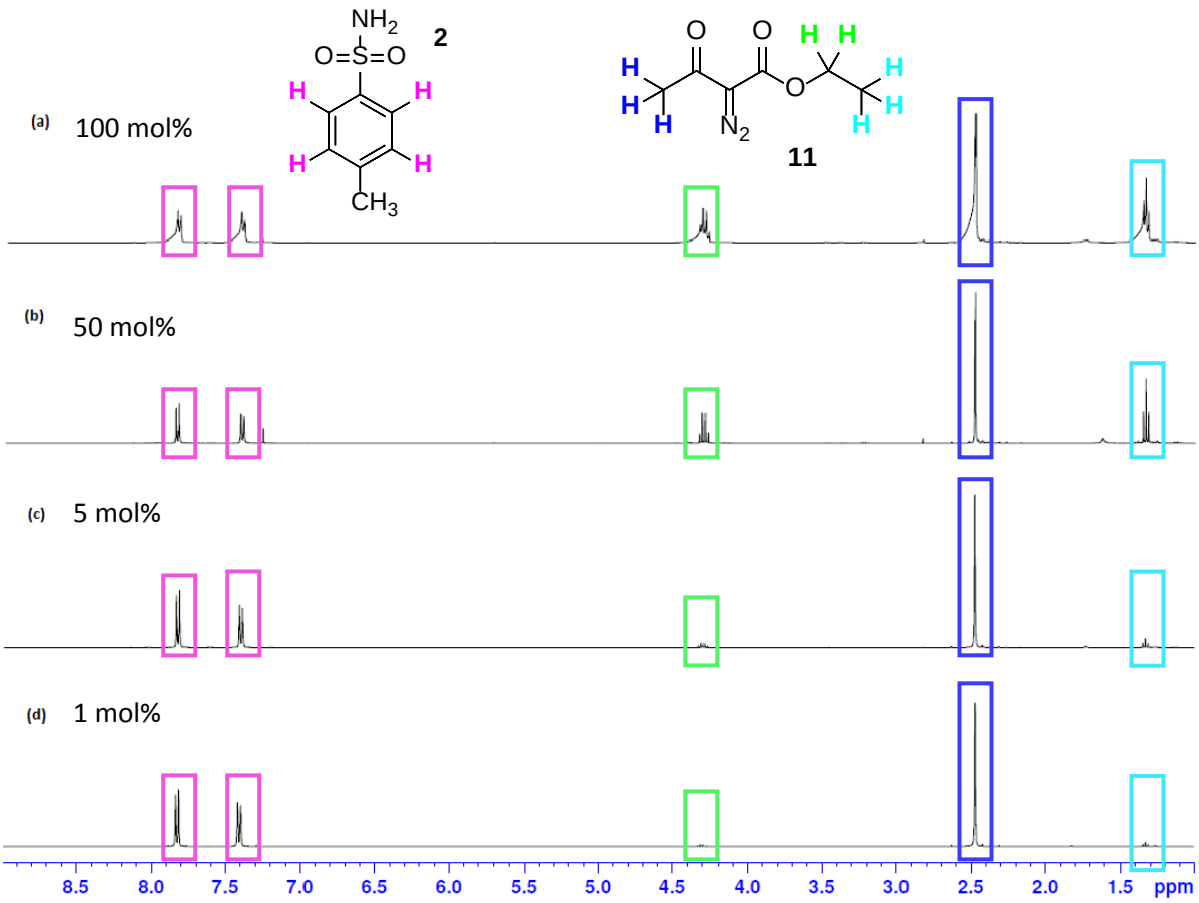


Figure 2.3 ^{1}H NMR spectra of the crude reaction mixtures for the following reactions: (a) 1 eq. **9** with 1 eq. **1** and 100 mol% Et_3N following a base work-up, (b) 1 eq. **9** with 1 eq. **1** and 50 mol% Et_3N following a base work-up, (c) 1 eq. **9** with 1 eq. **1** and 5 mol% Et_3N following a base work-up, (d) 1 eq. **9** with 1 eq. **1** and 1 mol% Et_3N following a base work-up.

As can be seen from **Figure 2.3**, although there is no evidence of a CH_2 singlet at δ_H 3.5 ppm to indicate remaining starting material, the quantity of product in the NMR sample is decreasing as the base loading decreases. In addition, the amount of what was thought to be at the time *p*-toluenesulfonamide **2** remaining is substantial in all cases, despite a 9% KOH wash, which is intended to remove the sulfonamide by-product (see pg. 89). It was decided to repeat these reactions, but to obtain a ^{1}H NMR spectrum of the crude reaction mixture after the solvent had been removed and without any KOH wash. The results are shown below in **Figure 2.4**.

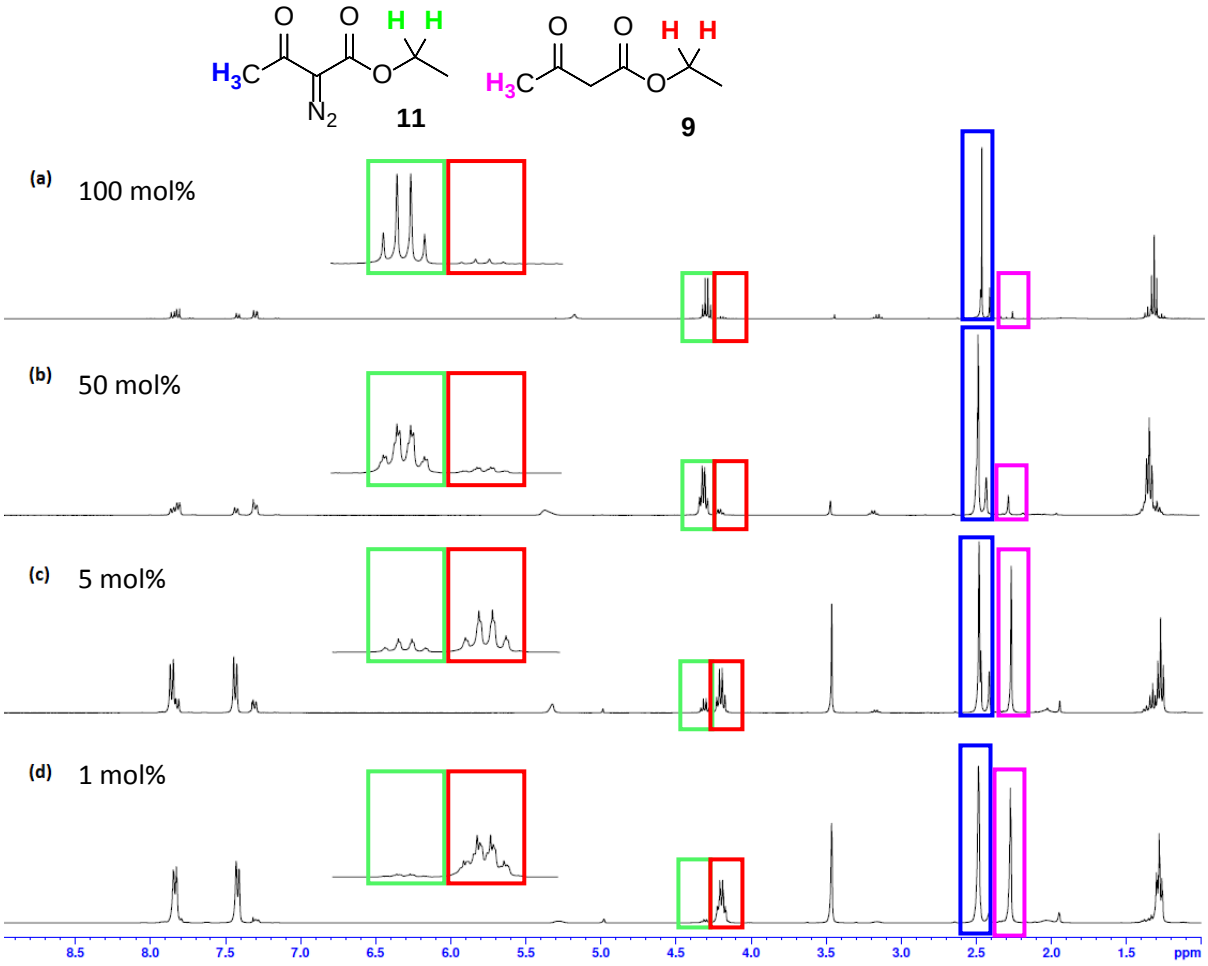
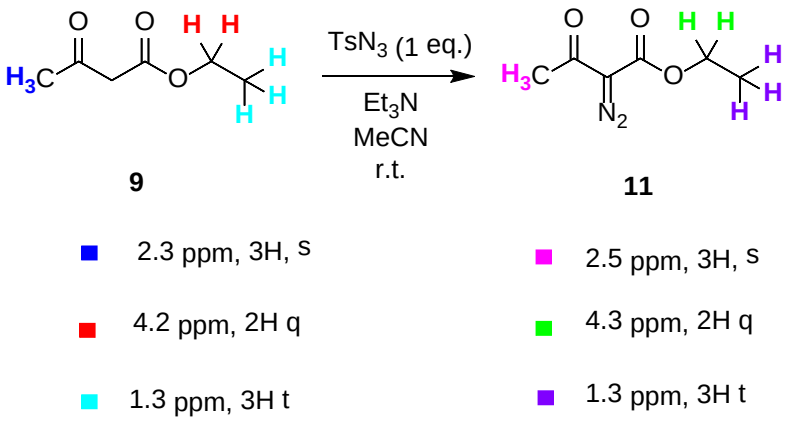


Figure 2.4 ^{1}H NMR spectra of the crude reaction mixtures for the following reactions: (a) 1 eq. **9** with 1 eq. **1** and 100 mol% Et_3N prior to work-up, (b) 1 eq. **9** with 1 eq **1** and 50 mol% Et_3N prior to work-up, (c) 1 eq. **9** with 1 eq. **1** and 5 mol% Et_3N prior to work-up, (d) 1 eq. **9** with 1 eq. **1** and 1 mol% Et_3N prior to work-up.

As seen from the expansion of the region δ_H 4-4.5 ppm, there is now evidence of two distinct quartets. The quartet at δ_H 4.2 ppm corresponds to the CH_2 of the ethyl group of the β-ketoester **9**, and the second quartet at 4.3 ppm corresponds to the CH_2 of the ethyl group of the α-diazo β-ketoester **11** (**Scheme 2.8**). As can be seen above, the CH_3 group of the methyl ketone also indicates reaction completeness; the signal at δ_H 2.25 ppm corresponds to **9** and the signal at δ_H 2.45 corresponds to **11**.

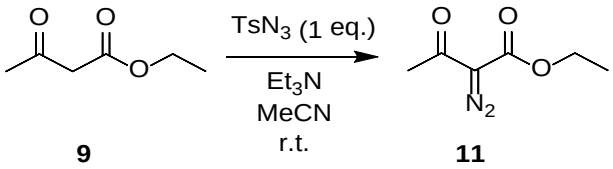


Scheme 2.8

As can be seen from **Figure 2.4**, when the reaction is carried out with one full equivalent of triethylamine, the major component of the reaction mixture is α-diazo-β-ketoester product, with very little evidence of any starting material remaining at δ_H 3.5 ppm. Two distinct sets of aromatic signals in the δ_H 7.0-8.0 ppm region can also be seen (see pg. 89 for further discussion). At 50 mol% loading of triethylamine, some starting material remains, however conversion to the desired product **11** is high.

When the base loading is lowered to 5 mol% triethylamine, a switch in the ratio of starting material to product is observed, with starting material now being the major component. Finally, when the reaction was carried out with just 1 mol% loading of triethylamine, very little product is observed, and the second set of aromatic signals in the δ_H 7.0-8.0 ppm region has almost disappeared. Due to the distinct shift downfield of this quartet from the starting material, it is possible to accurately calculate conversion from starting material to product. This is often difficult in diazo transfer reactions, as the disappearance of the CH_2 signal is indicative of reaction completion, rather than the appearance of a new signal. The results are displayed in **Table 2.6**. Further studies with ethyl acetoacetate **9** will be examined in **Section 2.3.3**.

Table 2.6 ***Base loading screen with no KOH wash***



9 **11**

Entry	*Reaction Time*	*Et_3N Loading*	*Concentration*	*Conversion*[1]
1	5h	100 mol%	0.10 mol/ L	93%
2	5h	50 mol%	0.11 mol/ L	86%
3	5h	5 mol%	0.11 mol/ L	24%
4	5h	1 mol%	0.11 mol/ L	8%

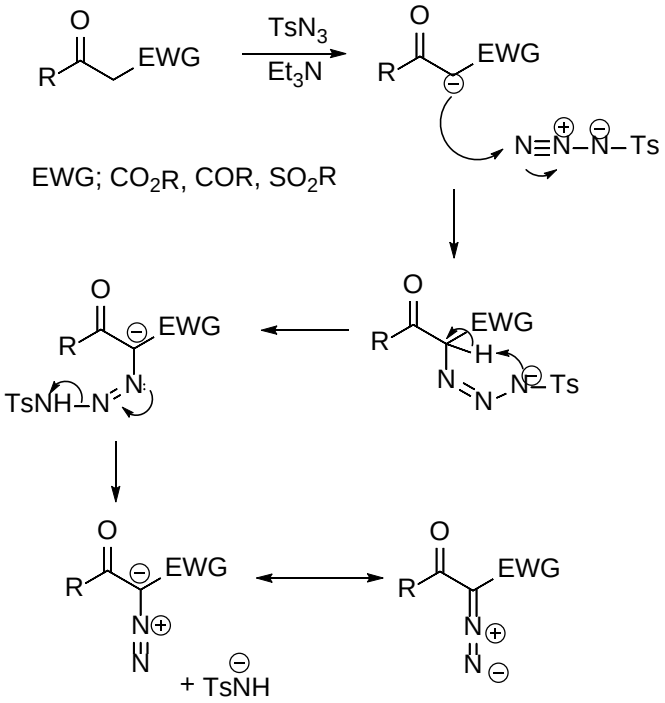
[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

From this series of experiments, a number of important conclusions were reached. Two sets of aromatic signals were observed in the δ_H 7.0-8.0 ppm region when no base wash was carried out. One set is from the *p*-toluenesulfonamide by-product, while the second set is from unreacted *p*-toluenesulfonyl azide **1** in the reaction mixture. It was determined that the signals δ_H 7.4-7.9 ppm along with a singlet at δ_H 2.46-2.47 ppm correspond to the *p*-toluenesulfonyl azide. This singlet was determined to appear at the same position at the CH_3 singlet of **11**, therefore it is not distinguishable in **Figure 2.3** (pg. 86). The signals from δ_H 7.3-7.8 ppm and the singlet at δ_H 2.43-2.44 ppm correspond to the *p*-toluenesulfonamide by-product.

Careful examination of the spectra of the initial reactions revealed that what had been assumed to be sulfonamide (signals in pink, **Figure 2.3**) which had not been removed by the work-up was in fact unreacted azide. Therefore, the 9% KOH wash does, in fact, remove the *p*-toluenesulfonamide by-product **2** from the reaction mixture, as well as any unreacted starting material, leaving behind the diazo product and unreacted *p*-toluenesulfonyl azide **1**. This explains the unusual results from the reactions with a KOH wash; although no starting material was observed, the amount of product appeared to be decreasing as the base loading

was decreased. Now it can be seen that there was in fact less product being produced at the lower base loading, but that the starting material was being removed in the KOH wash. Therefore, when examining conversions for screening studies it is important not to carry out a KOH wash during work-up. To isolate pure product, a KOH wash is necessary.

Diazo transfer has always been accepted to be a stoichiometric reaction which requires one molecule of base to deprotonate each molecule of ester or other substrate to be deprotonated (**Scheme 2.9**). We were able to determine this is not the case, as when 5 mol% of base is used a maximum conversion of 5% to the α-diazo β-ketoester would be expected.



Scheme 2.9

However what is actually observed is 24% conversion to the desired product after 5 h. This implies that the triethylamine is somehow being recycled in order to deprotonate another molecule of ester. A possible mechanism for this is suggested below in **Figure 2.5**. This will be examined in more detail in **Section 2.6**.

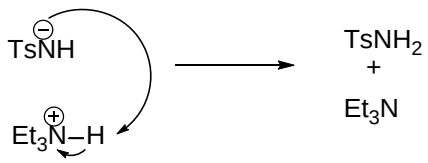
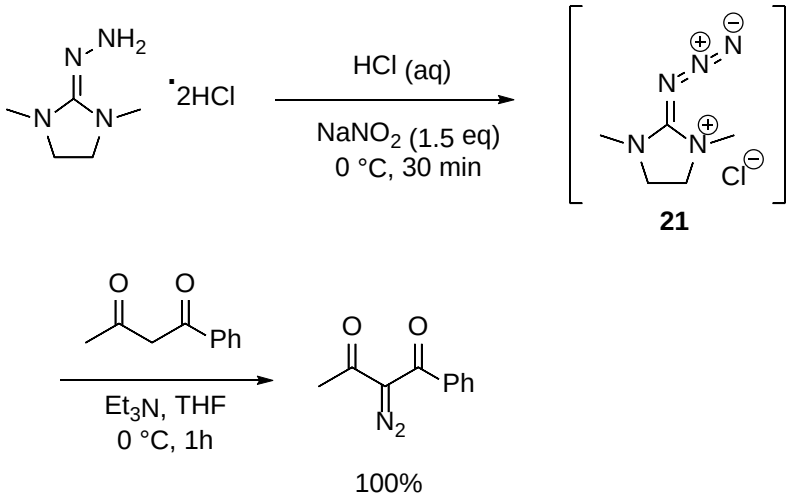


Figure 2.5 Postulated mechanism by which base may be regenerated.

2.3.4 Investigation into effects of solvent/base choice

Following on from our investigations into the reactivity of dimedone **20** in **Section 2.3.2** above, it was decided to use this as a model substrate to continue investigations into various parameters in the diazo transfer reaction, in particular the examination of the effect of choosing various bases and solvents on the efficacy of the reaction. Dichloromethane and acetonitrile are the conventional choice of solvents for diazo transfer in the literature, so they were included in the screen. In our efforts to move towards a "greener" process, some environmentally-friendly solvents were also selected.

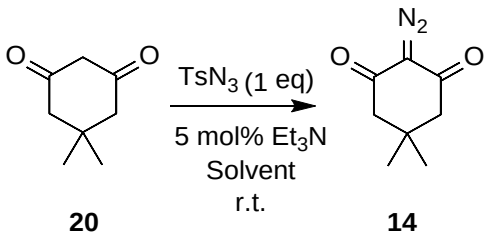
As discussed in **Section 2.3.2**, Ramachary and co-workers carried out diazo transfer in ionic liquids.[24] The next logical step was, it seemed, to attempt diazo transfer in water. Although to our knowledge there is no record in the literature of diazo transfer using water as reaction solvent, Kitamura *et al*. reported the generation of 2-azido-1,3-dimethylimidazolinium chloride (ADMC) **21** in aqueous hydrochloric acid.[25] Upon formation of this diazo transfer reagent, the diketone substrate was added to solution. However, it was only when tetrahydrofuran was added as a co-solvent that this was successfully optimised, as shown in **Scheme 2.10**. The optimal method was determined to be addition of substrate and base in THF and/or acetonitrile and where the reagent is not sulfonyl azide-based, the by-products are highly soluble in water.



Scheme 2.10

Ethanol was also chosen as an additional "green" solvent. The bases selected to examine were the most widely used bases for diazo transfer to various functional groups; triethylamine, DMAP and potassium carbonate. Firstly, the effects of various solvents on the reaction were examined, keeping all other parameters constant. The reactions were monitored by TLC, and were found to require approximately 18 h for complete consumption of **20**.

Table 2.7 ***Dimedone reactions with catalytic quantity of triethylamine***



Entry	***Solvent***	***Volume***	***Time***	***Yield[1]***
1	Acetonitrile	5 mL	18 h	96%[2]
2	Dichloromethane	5 mL	18 h	64%
3	Water	5 mL	18.5 h	51%
4	Ethanol	5 mL	18 h	68%

[1] % Yields reported following column chromatography on silica gel.

[2] This sample contained ~5% *p*-toluene sulfonamide **2**.

Although dimedone **20** was chosen as a model substrate, in hindsight, it is not an ideal choice, as due to its structure it is difficult to measure conversion for this reaction. As can be seen from **Figure 2.6**, a key proton shift change is not evident between starting material and product in this system, although the CH_2 signal at δ_C 57 ppm in the ^{13}C NMR spectrum does disappear following transfer of a diazo group. This means conversion can only be judged by the disappearance of the CH_2 peak at δ_H 3.26 ppm. Due to the difficulty associated with judging conversion from dimedone to 2-diazo-5,5-dimethylcyclohexane-1,3-dione **14**, all samples were purified by column chromatography on silica gel using hexane: ethyl acetate 80:20, and the isolated yields were used to compare results.

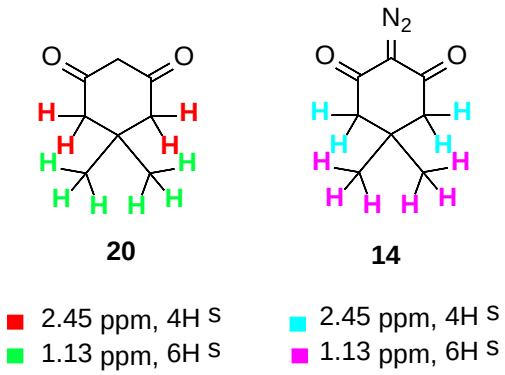


Figure 2.6 Key ^1H NMR signals of **20** and **14**.

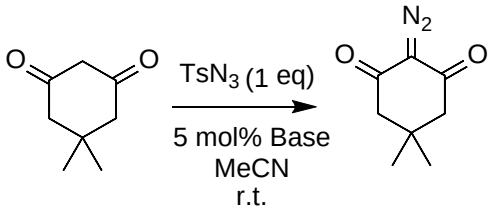
As can be seen from **Table 2.7**, all reaction conditions were kept constant, except for the solvent used. Under these reaction conditions, acetonitrile performed excellently, with >90% yield.

As mentioned in **Section 2.1**, some previous work within the group reported successful diazo transfer to β-ketoesters in water. This work is a more detailed and comprehensive study of initial work done by Tarrant.[14] In this instance 2-diazo-5,5-dimethylcyclohexane-1,3-dione **14** was obtained in 51% yield when the reaction was carried out in water. This is an excellent starting point for this project, which aims to optimise this process. It was decided to proceed with all four solvents for the base screen as, with the exception of acetonitrile, all yields obtained were comparable.

A slight change to the procedure was required for any reactions carried out in water. In all other cases the solvent for the reaction is removed under reduced pressure. This is not possible with water due to the fact that high temperatures are required for removal of water *in vacuo* and there may be unreacted tosyl azide **1** in the reaction flask if the reaction has not gone to 100% completion. Therefore the reaction mixture was transferred into a separating funnel, and extracted with 3 x 15 mL aliquots of ethyl acetate. The organic layers were then combined and washed with 20 mL of brine, before being concentrated *in vacuo*.

The next step was to examine the effect of altering the base on the efficiency of the reaction. In **Table 2.8** below, the results of the experiments done in acetonitrile are outlined. The best results were obtained with DMAP and triethylamine. Trace amounts of *p*-toluenesulfonyl amide **2** remained following column chromatography (entries 1 and 2), however problematic separation of *p*-toluenesulfonamide **2** from diazo products is one of the main difficulties associated with its use.[26] Excellent yields were obtained using both DMAP and triethylamine, as can be seen in **Table 2.8** (Entries 1 and 2). Potassium carbonate gave the worst results of the bases tested. Acetonitrile is a polar aprotic solvent with a dipole moment of 3.92 D,[27] which allows it to dissolve a wide range of ionic and non-polar compounds, however the solubility of potassium carbonate in acetonitrile is very poor.[28]

Table 2.8 ***Dimedone reactions in acetonitrile***



20 **14**

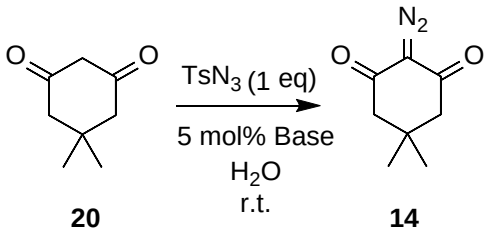
Entry	***Volume***	***Time***	***Base***	***Yield[1]***
1	5 mL	18h	DMAP	98%[2]
2	5 mL	18h	Et_3N	96%[2]
3	5 mL	18h	K_2CO_3	57%

[1] % Yields reported following column chromatography on silica gel.

[2] These samples contain ~5% *p*-toluene sulfonamide.

When the reaction was carried out in water with various bases, potassium carbonate proved to be very effective, with 78% conversion to the desired product. This is not surprising due to the high solubility of potassium carbonate in water (1.12 g/mL).

Table 2.9 ***Dimedone reactions in water***

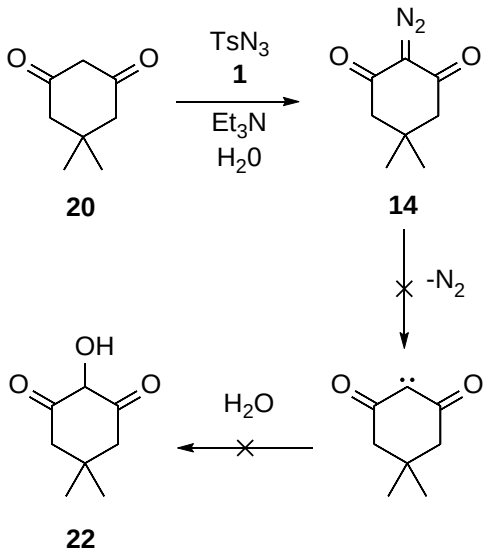


20 **14**

Entry	***Volume***	***Time***	***Base***	***Yield[1]***
1	5 mL	18h	DMAP	48%
2	5 mL	18h	Et_3N	51%
3	5 mL	18.5h	K_2CO_3	78%

1 % Yields reported following column chromatography on silica gel.

If any diazo product **14** were to decompose, the carbene generated in the reaction mixture from loss of diazo group could potentially result in the formation of the OH insertion product **22** by reaction with water (**Scheme 2.11**). However all reactions proceeded smoothly and no evidence of an additional product was seen in either TLC analysis or ^{1}H NMR spectroscopy of the crude product.

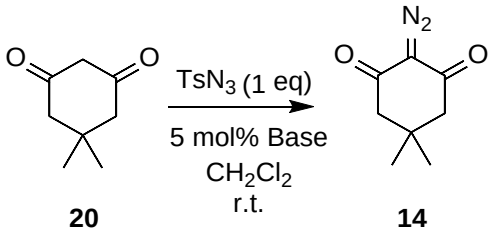


Scheme 2.11

It is interesting to note that when these reactions were carried out in water a creamy white solid was seen to form in the round bottomed flask as the reaction proceeded. This was thought to be the *p*-toluenesulfonamide **2** by-product, which is insoluble in water. It was envisioned filtration of the sulfonamide would give a simple route to purification, however this did not prove to be the case. **Entry 1** from **Table 2.9** above was repeated, and following 18.5 h the crude reaction mixture was filtered under vacuum using a Hirsch funnel. The cream solid was collected, and the filtrate was extracted into ethyl acetate as outlined above. When a ^{1}H NMR spectrum of the crude reaction mixture was obtained there was no evidence of the diazo product **14**.

The next solvent trialled in this screen was dichloromethane. Due to the fact that potassium carbonate had performed so poorly in acetonitrile, only triethylamine and DMAP were used in this screen. Although the yields obtained from these reactions were good, they were a substantial decrease from those obtained in acetonitrile.

Table 2.10 ***Dimedone reactions in dichloromethane***



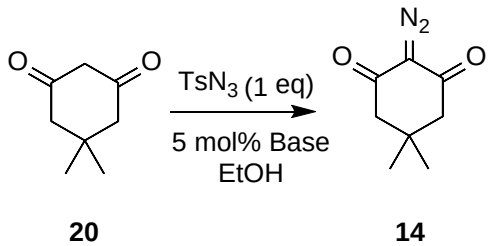
20 **14**

Entry	***Volume***	***Time***	***Base***	***Yield[1]***
1	5 mL	18.5h	DMAP	75%
2	5 mL	18h	Et_3N	64%

[1] % Yields reported following column chromatography on silica gel.

Ethanol was the final solvent used in this series of experiments. It was chosen as it is a polar aprotic solvent similar to water, and it is considered to be a green solvent in accordance with the 12 Principles of Green Chemistry as outlined by Anastas and Warner.[13] **Table 2.11** shows that the yields obtained when diazo transfer was carried out in ethanol were comparable to the yields obtained in dichloromethane, but with the advantage of avoiding the use of a chlorinated solvent.

Table 2.11 ***Dimedone reactions in ethanol***



20 **14**

Entry	***Volume***	***Time***	***Base***	***Yield[1]***
1	5 mL	18h	DMAP	72%
2	5 mL	18h	Et_3N	68%

[1] % Yields reported following column chromatography on silica gel.

As mentioned above, the problems associated with purification of reaction mixtures containing *p*-toluenesulfonamide **2**, or unreacted *p*-toluenesulfonyl azide **1** if present, and diazo products have been reported in the literature.[26] TLC analysis of a column from one of the above reactions in **Table 2.11** is shown in **Figure 2.7**. A large portion of diazo product **14** co-elutes with *p*-toluenesulfonamide **2**. Therefore comparing these reactions using isolated yields is potentially obscuring the results, as varying amounts of the diazo product may be co-eluting in different reactions. Although Presset and co-workers reported the use of consecutive silica and alumina columns as a means to fully separate various diazo compounds from *p*-toluenesulfonamide **2**,[26] this is a very labour intensive route for our purposes. At this point, it was evident that in the context of the study to be carried out, it is necessary to be able to clearly study the conversion from starting material to product. Therefore substrates which exhibit distinct signal changes in the ^{1}H NMR spectrum between the starting ester and the resulting diazo product were chosen for this study.

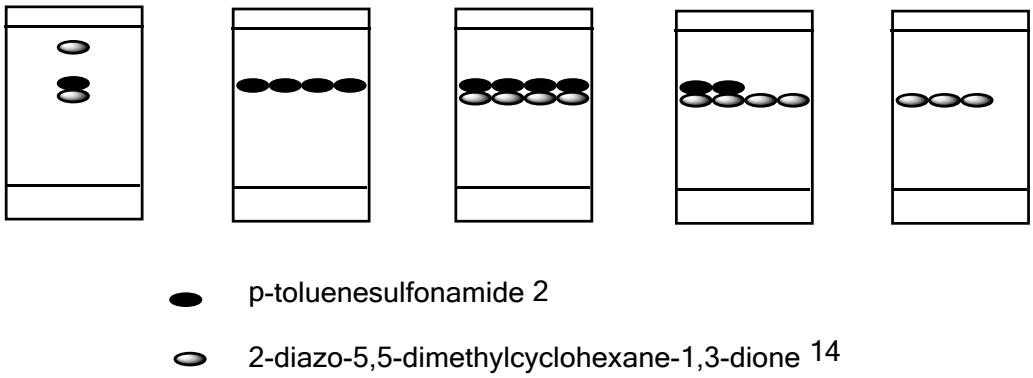
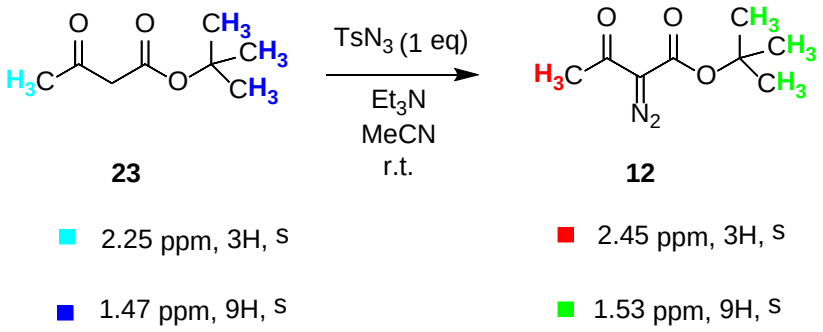


Figure 2.7 TLC analysis (in 80:20 hexane-ethyl acetate) of the crude reaction mixture of a diazo transfer reaction to **20**.

As can be seen from **Scheme 2.12**, *t*-butyl acetoacetate **23** has distinctly different signals in a ^{1}H NMR spectrum from *t*-butyl 2-diazo-3-oxobutanoate **12**. The protons of the methyl ketone appear at δ_H 2.25 ppm in the starting material, and at δ_H 2.45 ppm in the diazo product. In addition to this, the 9H singlet associated with the *t*-butyl group shifts from δ_H 1.47 ppm to δ_H 1.53 ppm following the diazo transfer reaction. This means that from the ^{1}H NMR spectrum of the crude reaction mixture it is possible to quantitatively measure the conversion from β-

ketoester **23** to α-diazo-β-ketoester **12**, therefore it was decided to use this substrate as a good model going forward.

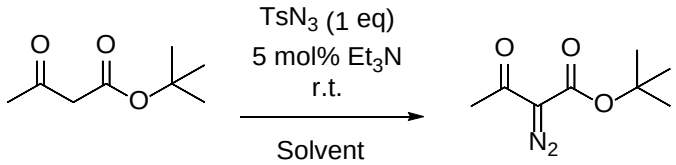


Scheme 2.12

It should be noted that this is an initial study to determine the optimal conditions for diazo transfer to β-ketoesters *via* a high throughput screening method. Therefore it was not practical to spend an inordinate amount of time carrying out column chromatography on each sample from every reaction in order to obtain yields of non-novel compounds from a large volume of experiments. Therefore conversions are used to compare the efficacy of various reaction conditions in the course of these screens.

The following study was carried out on *t*-butyl acetoacetate **23** where choice of base, choice of solvent, concentration, base loading and reaction time for the diazo transfer reaction were examined. The initial parameter to be examined was choice of base, and as can be seen from **Table 2.12** triethylamine was the first base tested. The only condition varied was the solvent being used. All reactions were carried out at room temperature under an inert atmosphere.

Table 2.12 ***t-Butyl acetoacetate reactions with triethylamine***



23 **12**

Entry	*Solvent*	*Volume*	*Time*	*Conversion*[1]
1	Acetonitrile	5 mL	20h	93%
2	Dichloromethane	5 mL	20.5h	97%[2]
3	Water	5 mL	20h	60%
4	Ethanol	5 mL	21h	–[3]

[1] Conversions calculated from ratio of starting material to product using 9H singlet of *t*-butyl group in the ^{1}H NMR spectrum of the crude reaction mixture.

[2] Singlets observed at 1.6 ppm and 2.7 ppm which do not correspond to any reagents or expected by-products of the reaction (~10%).

[3] No starting material remains, however unknown compound in crude reaction mixture with peaks at 1.38 ppm (t), 1.58 ppm (s) 2.79 ppm (s) and 3.17 ppm (q) – see pg. 103-104 for discussion.

The ^{1}H NMR spectrum of the crude reaction mixture of **Table 2.12**, Entry 3 is shown below in **Figure 2.8**. The ^{1}H NMR spectrum of Entry 3 is a typical example of a spectrum of a crude reaction mixture of a diazo transfer reaction. In the case of *t*-butyl acetoacetate **23**, the 2H singlet at δ_H 3.36 ppm corresponds to the α-hydrogens between the ketone and the ester carbonyls. In the aromatic region, there are four sets of doublets between δ_H 7-8 ppm. These correspond to the *para*-substituted rings of both *p*-toluenesulfonamide **2** and *p*-toluenesulfonyl azide **1** as shown in **Figure 2.8**.

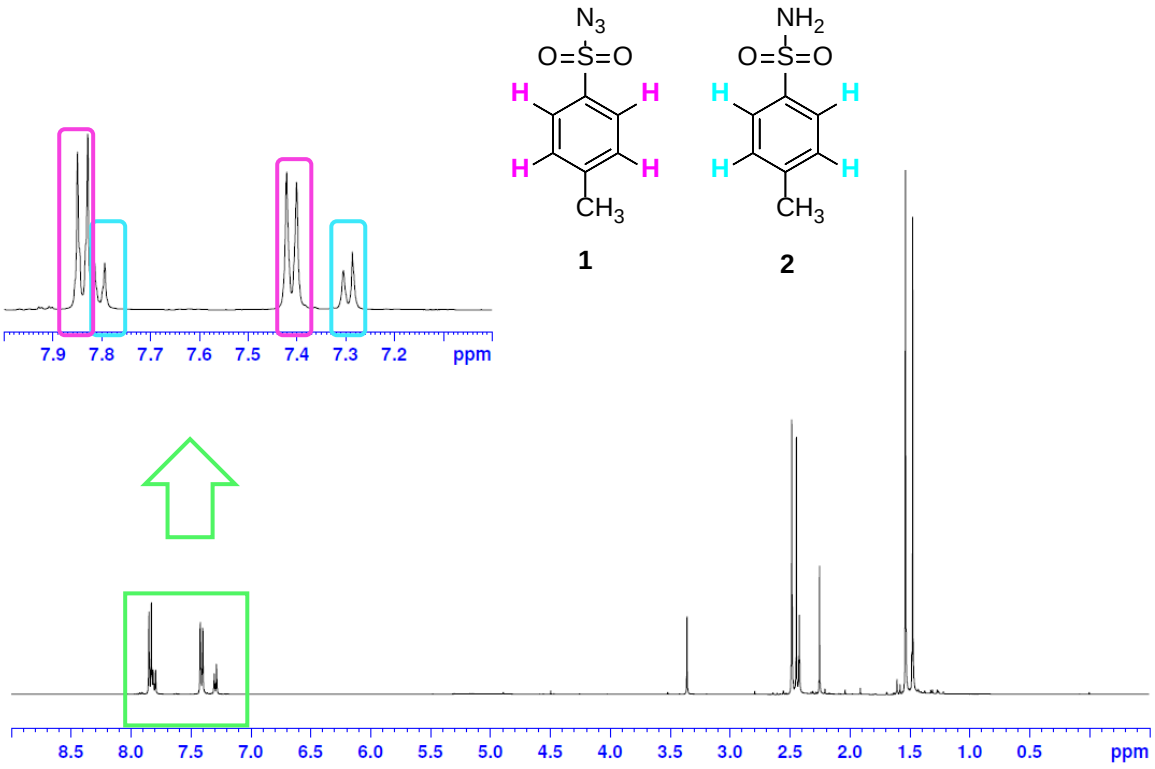


Figure 2.8 ^{1}H NMR spectrum of the crude reaction mixture for the following reaction: 1 eq. ethyl acetoacetate **9** with 1 eq. *p*-toluenesulfonyl azide and 5 mol% Et_3N in water.

Figure 2.9 shows an expansion of the region from δ_H 2.0-3.0ppm. This region contains four singlets – one each corresponding to *p*-toluenesulfonyl azide **1**, *t*-butyl acetoacetate **23**, *p*-toluenesulfonamide **2** and *t*-butyl 2-diazo-3-oxobutanoate **12**.

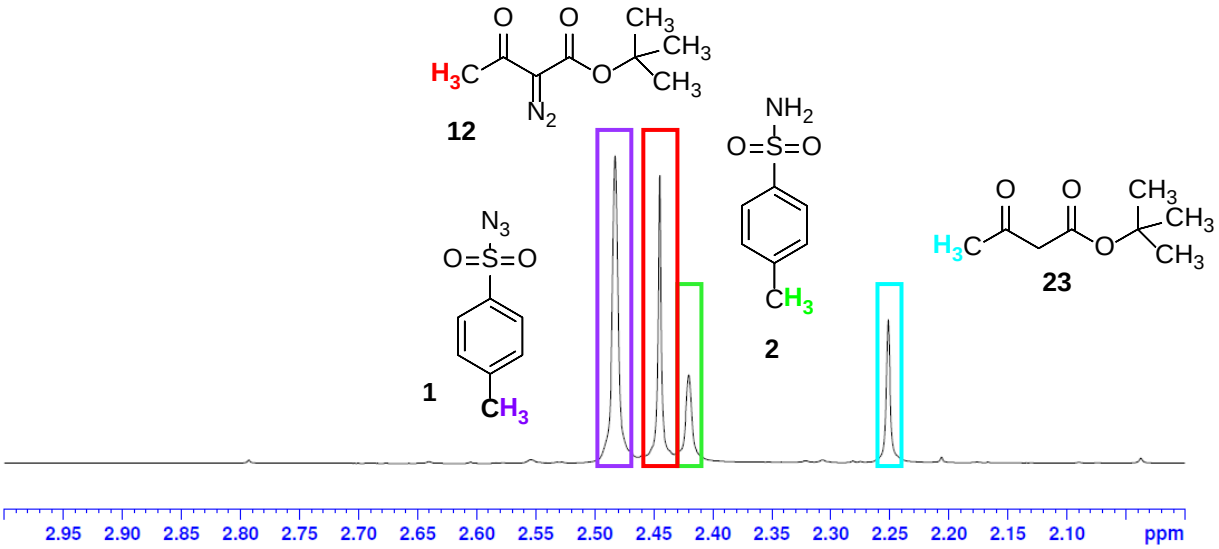


Figure 2.9 ^{1}H NMR spectrum of the crude reaction mixture of the following reaction: 1 eq. ethyl acetoacetate **9** with 1 eq. *p*-toluenesulfonyl azide and 5 mol% Et_3N in water – expansion.

The 9H singlet representative of the *t*-butyl group of the ester starting material appears at δ_H 1.47 ppm, while the singlet corresponding to the same group in the diazo product is observed at δ_H 1.53 ppm. By comparing the signals at δ_H 1.47 and 1.53 ppm, a ratio for conversion from *t*-butyl acetoacetate **23** to *t*-butyl 2-diazo-3-oxobutanoate **12** can be determined: in this case 60%. This was a disappointing result as water performed significantly poorer as a solvent than acetonitrile, which gave a conversion of 93% (Entry 1, **Table 2.12**). The ^{1}H NMR spectrum of this Entry 1 is shown below in **Figure 2.10**. As can be seen below, the signals at δ_H 1.47, 2.25 and 3.36 ppm corresponding to *t*-butyl acetoacetate **23** have significantly diminished.

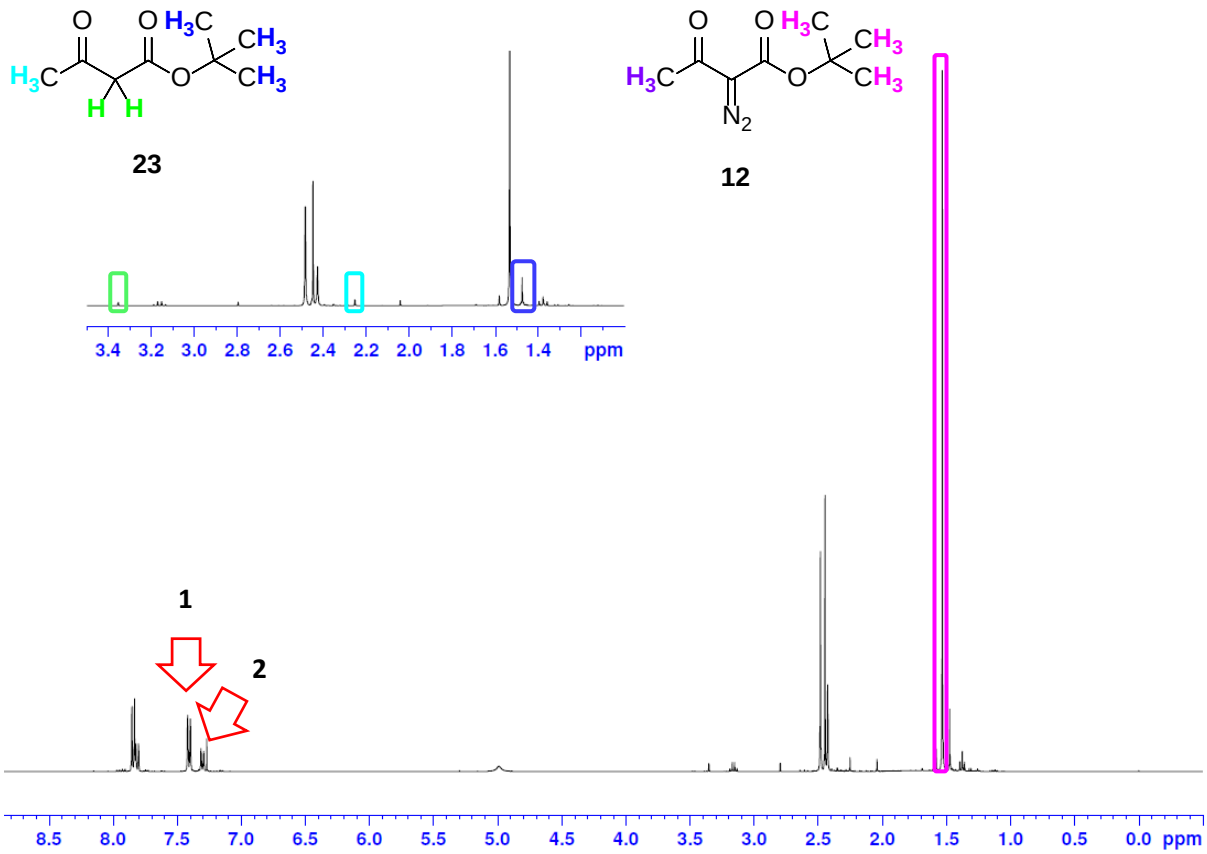


Figure 2.10 ^{1}H NMR spectrum of the crude reaction mixture of the following reaction: 1 eq. ethyl acetoacetate **9** with 1 eq. *p*-toluenesulfonyl azide and 5 mol% Et_3N in acetonitrile.

What is surprising about the spectrum in **Figure 2.10** is that the two sets of aromatic signals in the region of δ_H 7.2-7.9 ppm are just as prominent as those in **Figure 2.8**. As the reaction in **Figure 2.10** went to 93% completion, you would expect <10% *p*-toluenesulfonyl azide **1** to be present in the reaction mixture. While we were initially unsure of the meaning of this, after several different spectra from reactions carried out under varying conditions showed the same discrepancy it was inferred that the two compounds, *p*-toluenesulfonyl azide **1** and *p*-toluenesulfonamide **2**, have different solubilities in deuterated chloroform.

When dichloromethane was used as a solvent for this reaction (**Table 2.12**, Entry 2) an excellent conversion of 97% was achieved. However, two signals at δ_H 1.6 and 2.7 ppm appear in the ^{1}H NMR spectrum of the crude reaction mixture. These signals do not correspond to any expected product or by-product of this reaction. The signals are present at a low level (<10%) and are in a ratio of 3:1. These signals are so similar to those of *t*-butyl 2-diazo-3-

oxobutanoate **12** that the structure of the impurity is likely to have a general structure, as illustrated in **Figure 2.11**. A clearer example of this is seen later, in **Figure 2.24** (pg 134).

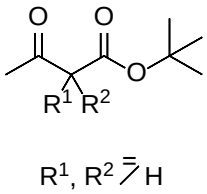
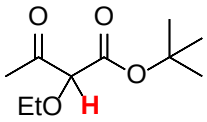


Figure 2.11

The last solvent chosen for the screen was ethanol (**Table 2.12**, Entry 4). Unexpectedly, when a ^{1}H NMR spectrum of the crude reaction mixture was obtained there was no evidence of either *t*-butyl acetoacetate **23** or *t*-butyl 2-diazo-3-oxobutanoate **12**, although the peaks corresponding to *p*-toluenesulfonyl azide **1** and *p*-toluenesulfonamide **2** were present. As well as those peaks, the following signals were observed: a 3H triplet at δ_H 1.38 ppm, singlets at δ_H 1.58 (~9H) and 2.79ppm (~3H) and a 2H quartet at δ_H 3.17 ppm. The source of these signals is not known, however one possibility we considered was loss of the diazo group, followed by OH insertion of a solvent molecule. Unfortunately, the peaks are not believed to correspond to the ethanol insertion product **24** shown in **Figure 2.12**, as the 1H singlet corresponding to the hydrogen indicated in red would be expected to appear in the region of δ_H 5 ppm according to similar compounds in the literature.



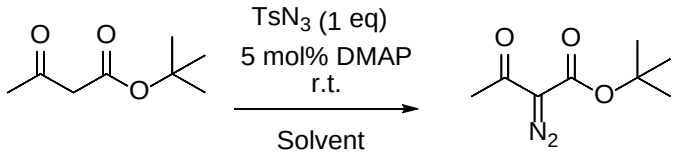
24

Figure 2.12

This initial screen showed that the use of dichloromethane and acetonitrile as solvents in the presence of triethylamine resulted in better conversions to the desired product than are observed when more polar solvents such as water and ethanol are used.

The next base assessed was DMAP (**Table 2.13**). Again, all other reaction conditions remained unchanged except for choice of solvent. As shown in **Table 2.13** DMAP is an exceptional choice of base, giving excellent conversions to *t*-butyl 2-diazo-3-oxobutanoate **12** in all cases.

Table 2.13 ***t-Butyl acetoacetate reactions with DMAP***



23 **12**

Entry	***Solvent***	***Volume***	***Time***	***Conversion[1]***
1	Acetonitrile	5 mL	20h	99%
2	Dichloromethane	5 mL	20.5h	98%
3	Water	5 mL	20h	95%
4	Ethanol	5 mL	21h	100%

[1] Conversions calculated from ratio of starting material to product using 9H singlet of *t*-butyl group in the ^{1}H NMR spectrum of the crude reaction mixture.

The reactions were carried out at room temperature, under an inert atmosphere for approximately 20 h, at which time TLC analysis showed no evidence of any starting material remaining. As can be seen above, there is no significant difference in conversion for reactions carried out in acetonitrile or dichloromethane, whether triethylamine or DMAP is used. However, when the reaction is carried out in water, a considerable improvement is seen when the base is changed from triethylamine (**Table 2.12**, Entry 3) to DMAP (**Table 2.13**, Entry 3) as shown in **Figure 2.13**.

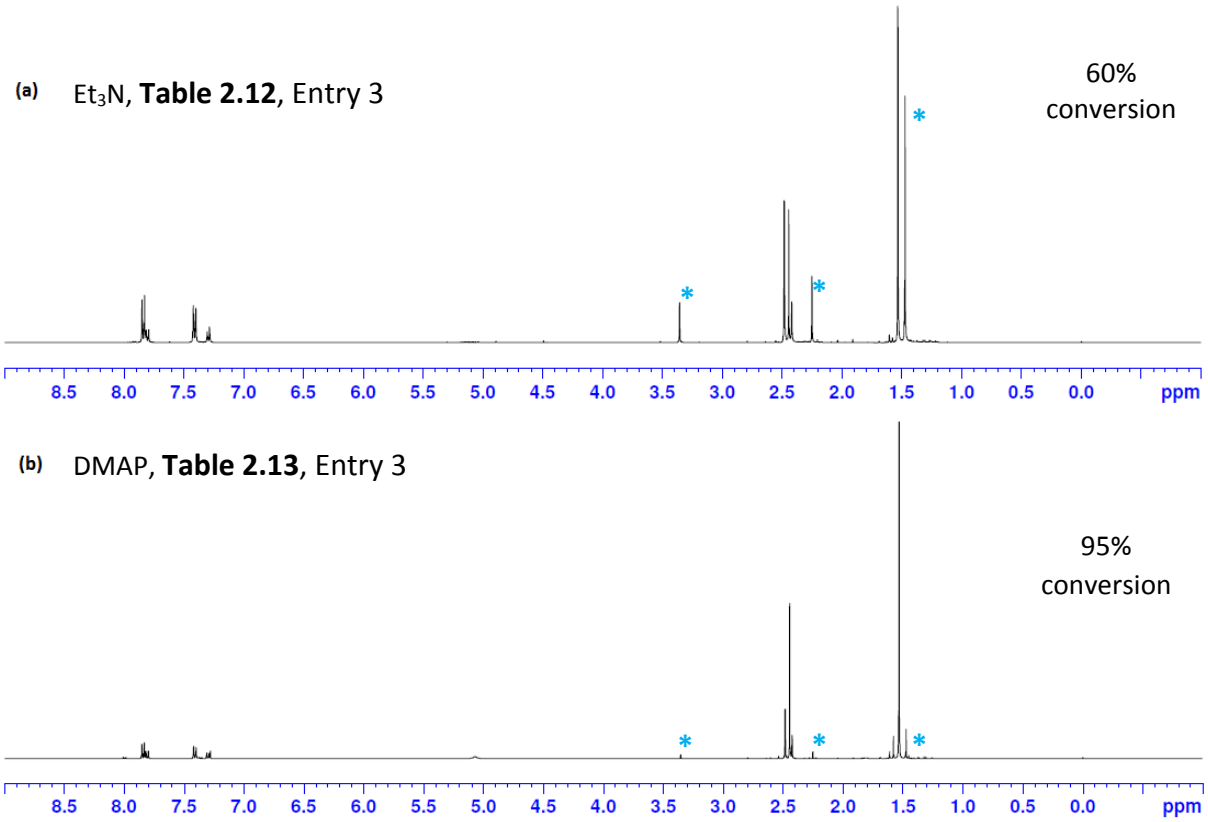
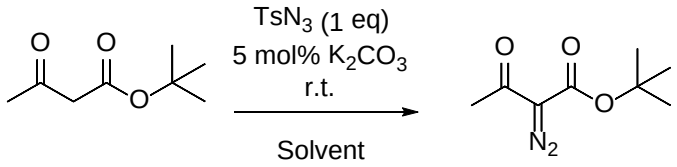


Figure 2.13 ^{1}H NMR spectra of the crude reaction mixtures of the following reactions: (a) 1 eq. **23** with 1 eq. **1** and 5 mol% Et_3N in water, (b) 1 eq. **23** with 1 eq. **1** and 5 mol% DMAP in water. Peaks corresponding to **23** are shown with *.

The most significant result obtained from this set of experiments is seen in Entry 4 of **Table 2.13**. 100% conversion to *t*-butyl 2-diazo-3-oxobutanoate **12** was obtained when DMAP was used as base in ethanol. This is especially noteworthy as when triethylamine is used for the same reaction, the desired product is not observed at all as outlined above.

Following on from the triethylamine and DMAP studies, it was decided to investigate the use of potassium carbonate as base. When the reaction was done in acetonitrile, the reaction proceeded with 90% conversion to the desired product after 20 hours at room temperature. However when the same reaction was done in water, the ^{1}H NMR spectrum showed evidence of only 14% *t*-butyl 2-diazo-3-oxobutanoate **12** present, as can be seen in **Table 2.14**.

Table 2.14 ***t-Butyl acetoacetate reactions with potassium carbonate***



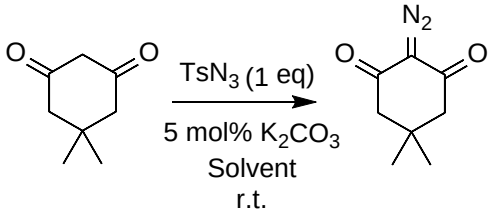
23 **12**

Entry	*Solvent*	*Volume*	*Time*	*Conversion*[1]
1	Acetonitrile	5 mL	20h	90%
2	Water	5 mL	20h	14%

[1] Conversions calculated from ratio of starting material to product using 9H singlet of *t*-butyl group in the ^{1}H NMR spectrum of the crude reaction mixture.

This is especially unusual when compared to the results obtained for the same screen on dimedone **20**, shown in **Table 2.15** below, particularly when comparing Entry 2 from **Table 2.14** with Entry 2 from **Table 2.15**. Although the results for dimedone **20** in **Table 2.15** are reported as yields rather than conversions, 2-diazo-5,5-dimethylcyclohexane-1,3-dione **14** must be formed with a very high conversion to obtain a 78% isolated yield. This highlights the difference between the behaviour of β-ketoesters in water compared to that of diketones in water, which is more pronounced when potassium carbonate is used as a base.

Table 2.15 ***Dimedone reactions with potassium carbonate***



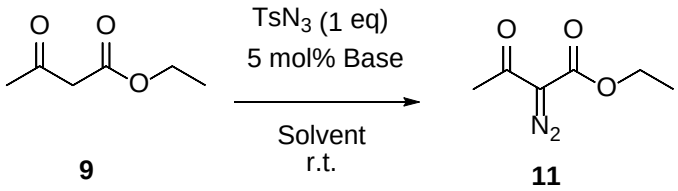
20 **14**

Entry	*Solvent*	*Volume*	*Time*	*Yield*[1]
1	Acetonitrile	5 mL	18h	57%
2	Water	5 mL	18h	78%

1 % Yields reported following column chromatography on silica gel.

Ethyl acetoacetate **9** was also used as a substrate for these initial investigations. As outlined previously in **Scheme 2.8** (pg. 88), its structural features are ideal for judging conversion to the diazo product **11** by ^{1}H NMR spectroscopy. **Table 2.16** outlines the experiments carried out with ethyl acetoacetate **9**, and as in the case of dimedone and *t*-butyl acetoacetate **23**, bases and solvents were varied while all other reaction parameters were kept constant.

Table 2.16 ***Ethyl acetoacetate reactions with 5 mol% of base***



9 **11**

Entry	***Solvent***	***Volume***	***Time***	***Base***	***Conversion[1]***
1	Acetonitrile	5 mL	20h	DMAP	95%[2]
2	Acetonitrile	5 mL	20h	Et_3N	82%
3	Dichloromethane	5 mL	20.5h	DMAP	95%[2]
4	Dichloromethane	5 mL	20.5h	Et_3N	28%[2]
5	Water	5 mL	20h	DMAP	73%
6	Water	5 mL	17h	Et_3N	11%
7	Ethanol	5 mL	21h	DMAP	74%[2]
8	Ethanol	5 mL	21h	Et_3N	74%
9	Acetonitrile	5 mL	20h	K_2CO_3	100%
10	Water	5 mL	20h	K_2CO_3	18%

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

[2] Unknown impurity (5%) with ethyl peaks at 1.4 ppm (t) and 4.4 ppm (q). Impurity not recovered following column chromatography on silica gel.

A number of conclusions may be taken from this set of experiments. Again, acetonitrile and dichloromethane performed excellently (**Table 2.16**, Entry 1 and 2), with 100% consumption of the starting material in the presence of DMAP, although <5% of an unknown impurity was observed (**Figure 2.14**). This is in stark contrast to the conversion achieved when triethylamine was used in conjunction with dichloromethane, only 28% conversion to the desired product was observed (**Table 2.16**, Entry 4). When the same reaction conditions were used for *t*-butyl acetoacetate, 97% conversion to the desired product was achieved (**Table 2.12**, Entry 2). Interestingly, these conditions also resulted in an unknown impurity with similar peaks to the product for *t*-butyl acetoacetate **23**, as shown in **Figure 2.11** – the corresponding unknown for ethyl acetoacetate **9** shown in **Figure 2.14**. This impurity was not recovered following column chromatography on silica gel.

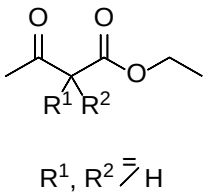


Figure 2.14

Entries 5 and 6 in **Table 2.16** above show a strong difference between conversions attained using DMAP and triethylamine in water. When 5 mol% triethylamine was used in water, only 11% conversion from ethyl acetoacetate **9** to ethyl 2-diazo-3-oxobutanoate **11** was observed. When repetition of this experiment confirmed its validity, it was decided that further investigation was required. This will be discussed in more detail in **Section 2.3.4**.

It is interesting to note that the conversions achieved with potassium carbonate for both ethyl acetoacetate **9** and *t*-butyl acetoacetate **23** compare remarkably well. This can be clearly seen when Entries 9 and 10 in **Table 2.16** (100% and 18% respectively) are compared with Entries 1 and 2 in **Table 2.14** (90% and 14% respectively).

Apart from not being considered a 'green' solvent, the use of dichloromethane on an industrial scale is generally avoided due to the health and safety concerns associated with

chlorinated solvents. When this was considered, in addition to the fact that conversions obtained in dichloromethane were at best, comparable to acetonitrile, it was decided to discontinue its use in further screens.

This was also true for ethanol, which was not as efficient a reaction solvent as acetonitrile or dichloromethane. Although a 'green' solvent, it was ultimately decided to proceed with only water and acetonitrile for the remaining screens.

2.3.4 Investigation of effects of dilution and base loading

At this point in the project, a discrepancy was noticed between two results previously obtained. In our initial base loading screen in **Section 2.3.3**, 24% conversion from ethyl acetoacetate **9** to ethyl 2-diazo-3-oxobutanoate **11** was observed when 5 mol% triethylamine was used in acetonitrile over 5h (**Table 2.6**, Entry 3). In a later screen in **Section 2.3.4**, 82% conversion from ethyl acetoacetate **9** to ethyl 2-diazo-3-oxobutanoate **11** was observed when 5 mol% triethylamine was used in acetonitrile over 20h (**Table 2.16**, Entry 2).

The reaction conditions of both reactions were compared, and it was noted that in addition to different reaction times, each reaction was carried out in a different volume of solvent. When carrying out the initial base screen in **Section 2.3.3**, all reactions were done in 15 mL of acetonitrile, while all subsequent screens were done using a 5 mL volume of the relevant solvent. It was unclear whether the increased concentration or the increased reaction time was resulting in the large increase in conversion from 24% to 82%. Therefore it was decided to attempt **Table 2.16**, Entry 2 again but with a reduced solvent volume of 1.5 mL acetonitrile. Gratifyingly, these conditions led to a 98% conversion to ethyl 2-diazo-3-oxobutanoate **11** (**Table 2.17**, Entry 2), and with this in mind, it was decided to explore this concentration effect further.

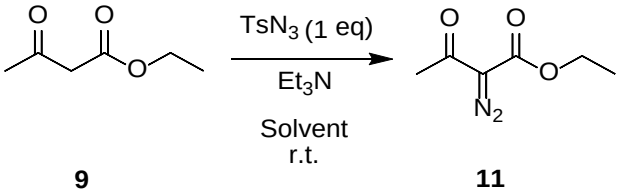
The next screen undertaken aimed to examine the effect of changing two parameters – base loading and concentration. Up until this point, each base had been used at a loading of 5 mol%, and reactions were typically carried out using approximately 100 mg of starting ester

in 5 mL of solvent – a concentration in the region of 0.16 mol/L, depending on starting substrate.

For the purpose of this screen it was decided to increase the base loading from 5 to 15 mol%. This was a sufficient increase to investigate if a higher base loading made a measurable difference in the efficacy of the reaction, while still remaining at a level low enough to be considered a significant reduction from the established procedure of one full equivalent.

The concentration was also increased threefold, from approximately 0.16 mol/L to 0.5-0.6 mol/L. Acetonitrile was chosen as a standard against which to compare water, as it is the conventional solvent for these reactions. The results are displayed below in **Table 2.17**.

Table 2.17 ***Ethyl acetoacetate reactions with varying concentration and base loading***



9 **11**

Entry	*Solvent*	*Volume*	*Time*	*Base Loading*	*Concentration*	*Conversion*[1]
1	CH_3CN	1.5mL	19h	5mol%	0.60 mol/L	98%
2	CH_3CN	5mL	20h	5mol%	0.15 mol/L	82%
3	CH_3CN	1.5mL	19h	15mol%	0.53 mol/L	100%
4	CH_3CN	5mL	20h	15mol%	0.16 mol/L	98%
5	H_2O	1.5mL	19h	5mol%	0.56 mol/L	94%
6	H_2O	5mL	17h	5mol%	0.17 mol/L	11%
7	H_2O	1.5mL	19h	15mol%	0.57 mol/L	96%
8	H_2O	5mL	20h	15mol%	0.18 mol/L	74%

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

There are several important points to take from this screen. If we first compare Entries 1 and 3, and 5 and 7 from **Table 2.17** we can see that at a higher concentration, increasing the base loading from 5 to 15 mol% has no significant impact, perhaps due the already very high conversions, as shown in **Figure 2.15**.

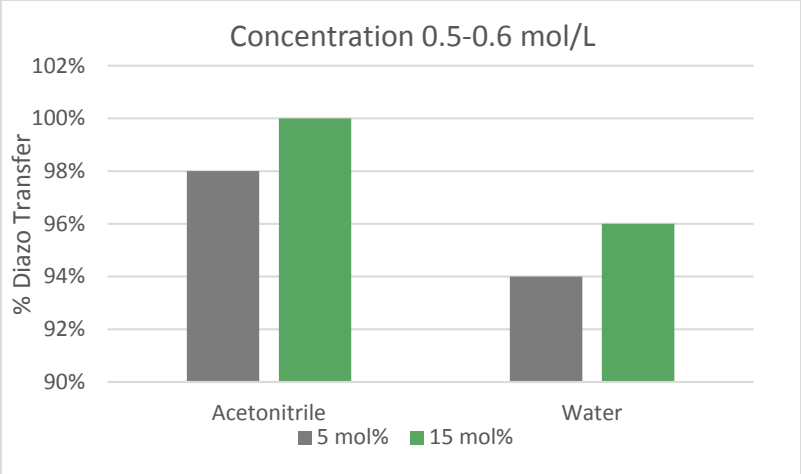


Figure 2.15 Chart showing % diazo transfer to **9** when varying loadings of Et_3N are used as base in water and acetonitrile at high concentrations.

At the lower concentration of approximately 0.16 mol/L the effect of increasing the base loading is more substantial. This may be seen when comparing Entries 2 and 4, and particularly 6 and 8 in **Table 2.17** above, or illustrated below in **Figure 2.16**.

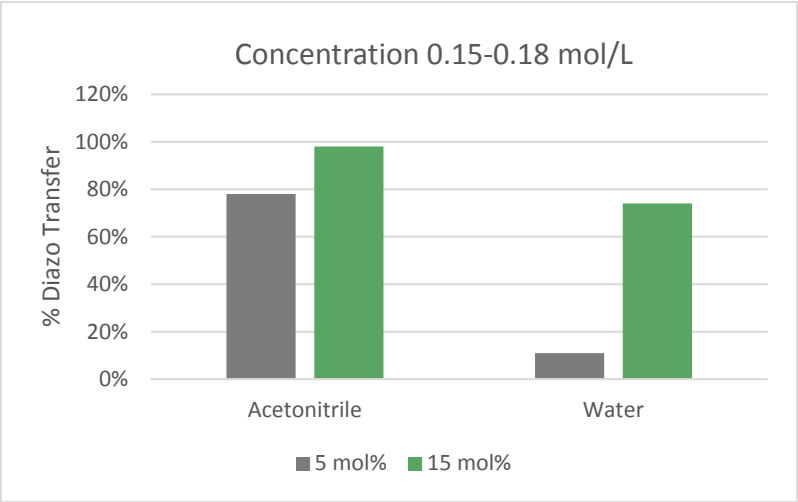


Figure 2.16 Chart showing % diazo transfer to **9** when varying loadings of Et_3N are used as base in water and acetonitrile at lower concentrations.

As shown in **Figure 2.16**, when the reaction is carried out in a higher volume of acetonitrile (5 mL) there is a 20% increase in diazo transfer when the base quantity is raised from 5 to 15

mol%. When the lower concentration was used for water, a large increase in conversion was seen going from 5 to 15 mol% of triethylamine.

The most significant result is seen when comparing the effect of increasing the concentration of the reaction mixture, as shown in **Figure 2.17**. At the higher base loading in acetonitrile (Entries 3 and 4, **Table 2.17**), excellent conversions are achieved at both lower and higher concentrations, suggesting that the effect of increasing the concentration seems to be nullified by a higher base loading. In this system, it seems that a point is reached where base loading has more of an impact on conversion than the concentration effect.

In contrast, in water the effect of altering the concentration is much more dominant, even with an increased base loading. When all other reaction parameters are kept constant, and the volume of solvent is decreased from 5 mL to 1.5 mL (Entries 7 and 8, **Table 2.17**) there is a 20% increase in conversion, a very significant improvement. It is clear that the concentration effect is more significant in water than in acetonitrile.

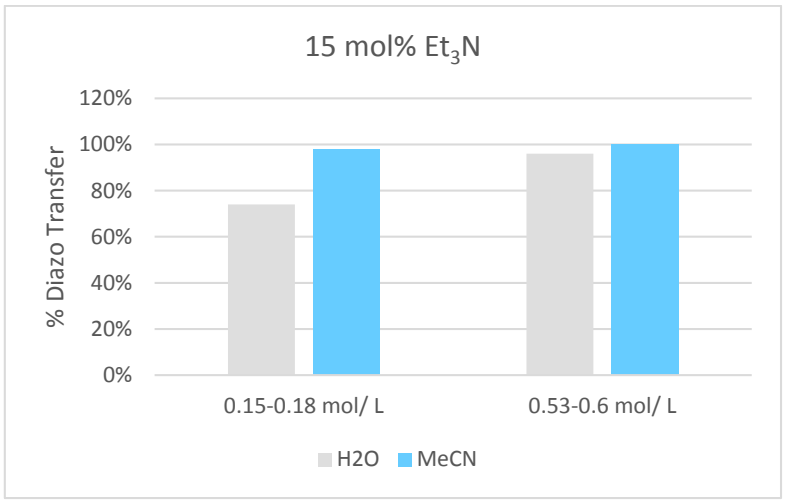


Figure 2.17 Chart showing % diazo transfer to **9** when 15 mol% Et_3N is used as base in water and acetonitrile at varying concentrations.

This effect is more dramatic when a lower base loading was used. In both acetonitrile and water, the increase in reactivity with a threefold decrease in solvent volume at 5 mol% base loading is pronounced, as can be seen in **Figure 2.18**. In acetonitrile, an increase of 20%, from

78% to 98% conversion is observed by simply decreasing the solvent volume from 5 mL to 1.5 mL.

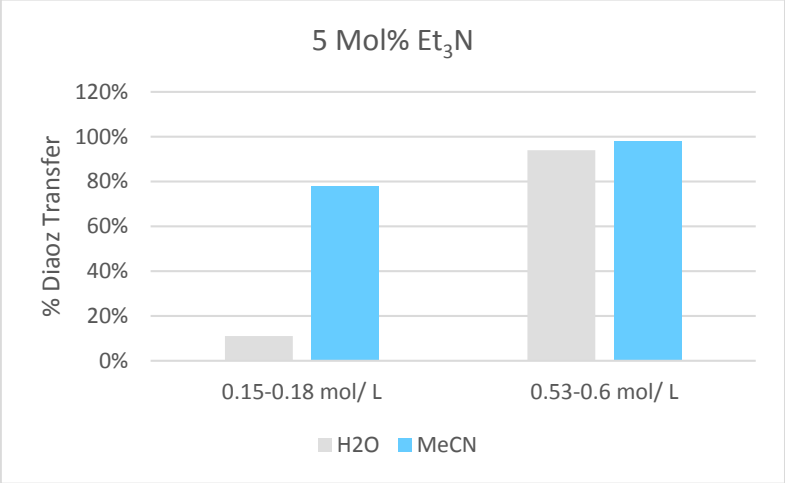


Figure 2.18 Chart showing % diazo transfer to **9** when 5 mol% Et_3N is used as base in water and acetonitrile at varying concentrations.

When this reaction is carried out in water, as we can see in the ^1H NMR spectra of the reaction mixtures (**Figure 2.19)**, concentration is extremely important. In a solvent volume of 5 mL (0.17 mol/L) with 5 mol% triethylamine, a conversion of only 11% is obtained (as previously observed in **Table 2.16**). However, when a solvent volume of 1.5 mL (0.56 mol/L) is used with all other conditions remaining the same, a conversion of 94% is observed. This unusual result merited repetition of the experiments three times and gave the same result in all cases.

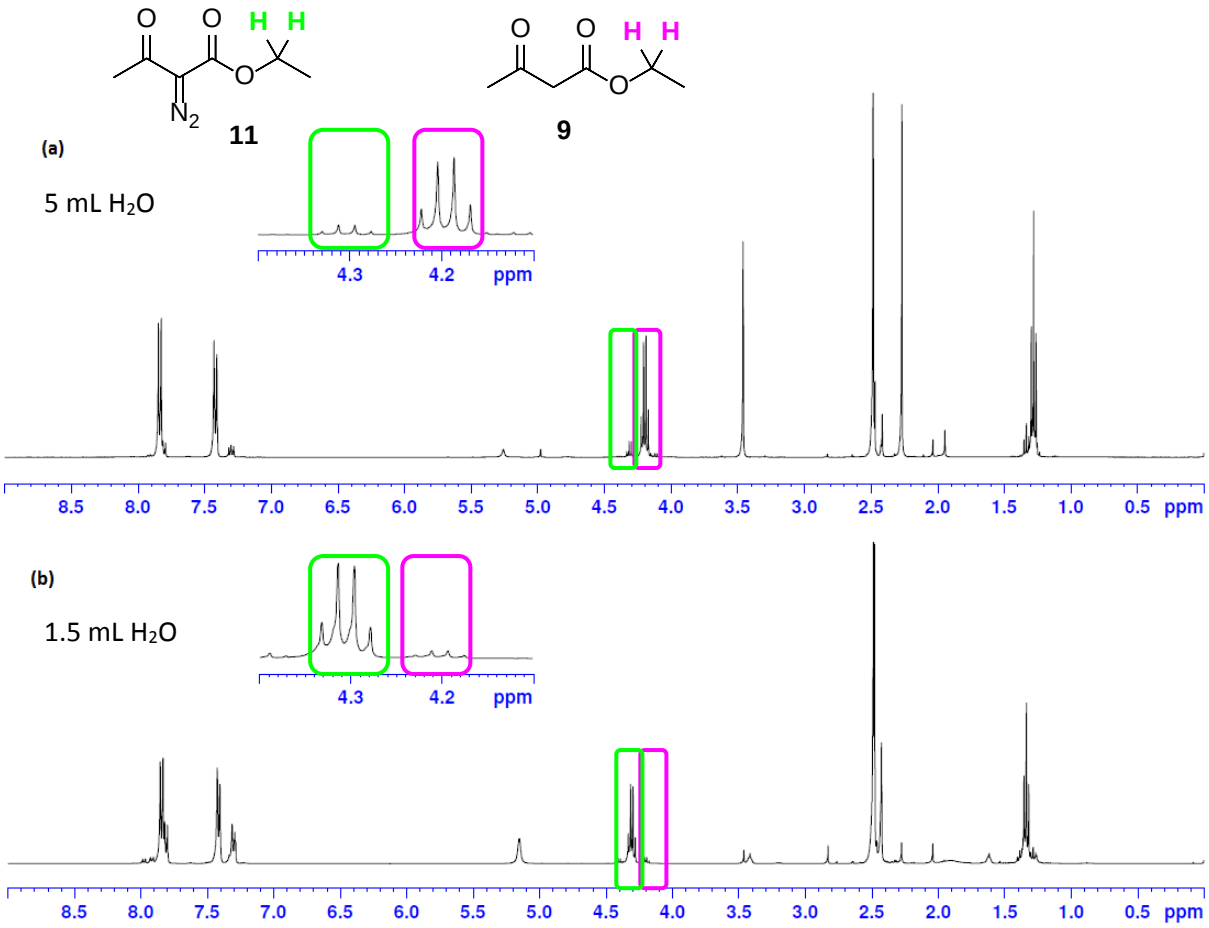
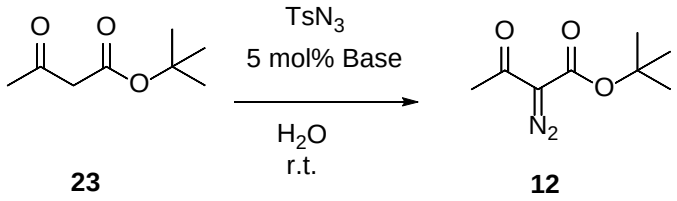


Figure 2.19 ^{1}H NMR spectra of the crude reaction mixtures of the following reactions: (a) 1 eq. ethyl acetoacetate **9** with 1 eq. **1** and 5 mol% Et_3N in 5 mL water, (b) 1 eq. ethyl acetoacetate **9** with 1 eq. **1** and 5 mol% Et_3N in 1.5 mL water.

With this in mind, it was decided to re-examine previous experiments to see if changing the concentration could improve results previously obtained. **Table 2.18** shows experiments done at higher concentrations for *t*-butyl acetoacetate **23** – for comparison purposes, the equivalent reactions carried out at lower concentrations are included.

Table 2.18 ***t-Butyl acetoacetate reactions at different concentrations***



Entry	*Volume*	*Concentration*	*Time*	*Base*	*Conversion*[1]
1	5 mL	0.14 mol/L	20h	DMAP	74%
2	1.5 mL	0.43 mol/L	20h	DMAP	95%
3	5 mL	0.13 mol/L	20h	Et_3N	60%
4	1.5 mL	0.44 mol/L	20h	Et_3N	100%
5	5 mL	0.14 mol/L	20h	K_2CO_3	14%
6	1.5 mL	0.45 mol/L	20h	K_2CO_3	9%

[1] Conversions calculated from ratio of starting material to product using 9H singlet of *t*-butyl group in the ^1H NMR spectrum of the crude reaction mixture.

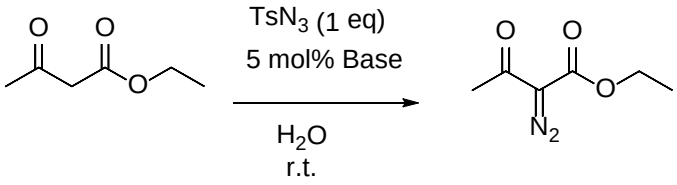
As can be seen above, in the case of potassium carbonate, increasing the increasing the concentration of the reaction does not increase the conversion to product. Although conversions for potassium carbonate are very low in both cases, a decrease is still observed when the concentration in increased from 0.14 mol/L to 0.45 mol/L.

Gratifyingly, DMAP was seen to follow the same pattern as triethylamine, with an increase in conversion to **12** observed when the concentration was increased (**Table 2.18**, Entries 1 and 2).

Similarly, a trend can also be seen when comparing the results obtained when using triethylamine as base. In **Table 2.18** above, 60% conversion to the desired product is obtained when a concentration of 0.13 mol/L is used (Entry 3). When the concentration is increased to 0.44 mol/L, 100% conversion to the desired product is observed (Entry 4). This significant increase of 40% in conversion when diazo transfer is done in water with 5 mol% of water in a

concentrated solution versus a dilute solution mirrors the results obtained for ethyl acetoacetate **9** in **Table 2.17** (Entries 5 and 6), where a 83% increase was seen. It was decided to carry out the same screen with ethyl acetoacetate **9**, the results of which are shown below in **Table 2.19**.

Table 2.19 ***Ethyl acetoacetate reactions at different concentrations***



23 **12**

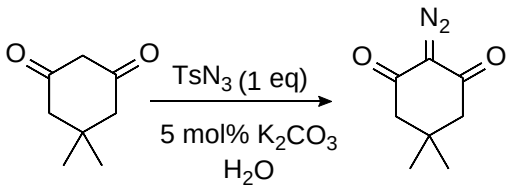
Entry	*Volume*	*Concentration*	*Time*	*Base*	*Conversion*[1]
1	5 mL	0.16 mol/L	20h	DMAP	73%
2	1.5 mL	0.52 mol/L	20h	DMAP	93%
3	5 mL	0.17 mol/L	17h	Et_3N	11%
4	1.5 mL	0.53 mol/L	20h	Et_3N	98%
5	5 mL	0.17 mol/L	20h	K_2CO_3	18%
6	1.5 mL	0.56 mol/L	20h	K_2CO_3	18%
7	20 mL	0.04 mol/L	20h	K_2CO_3	20%

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

The results for triethylamine have been discussed above, however in the case of ethyl acetoacetate **9** with DMAP (**Table 2.19**, Entries 1 and 2), an increase in conversion from 73% to 93% is observed when the concentration is increased from 0.16 mol/L to 0.52 mol/L. This is in agreement with the trend observed for *t*-butyl acetoacetate **23** above (**Table 2.18**, Entries 1 and 2).

In the case of potassium carbonate, there was no change in the amount of conversion observed when the concentration of the reaction was varied significantly. It was thought that, considering the results obtained for *t*-butyl acetoacetate **23**, perhaps potassium carbonate performs better under more dilute conditions. Therefore, the solvent volume was increased to 20 mL, a fourfold decrease in concentration, and again a similar conversion was obtained. It appears that regardless of the concentration of the reaction mixture, potassium carbonate in water doesn't significantly vary the efficiency of the diazo transfer reaction when β-ketoesters are used as substrate, never resulting in more than 20% conversion to the desired product. In a bid to further understand the somewhat unpredictable nature of this base, the diazo transfer reaction to dimedone **20** was also attempted at a higher concentration (**Table 2.20**).

Table 2.20 ***Dimedone reactions with potassium carbonate***



20 **14**

Entry	*Volume*	*Concentration*	*Time*	*Yield*[1]
1	5 mL	0.29 mol/L	18h	78%
2	1.5 mL	0.97 mol/L	18h	6%

[1] % Yields reported following column chromatography on silica gel.

As can be seen above, the same loading of potassium carbonate at a higher concentration resulted in a significant decrease in the yield of **14** for this reaction. This is in complete contrast to the results obtained with triethylamine and DMAP, and was initially thought to be an anomaly but several attempts gave the same poor yield.

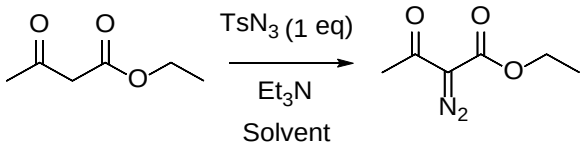
There also seems to be a significant difference between the behaviour of diketones and β-ketoesters in the presence of potassium carbonate and water. Due to the unpredictable and

poor results obtained with potassium carbonate for β-ketoesters, it was decided at this point to discontinue its use in this project.

2.3.5 Investigation into critical reaction parameters (base loading, time, solvent)

The final reaction parameter to be investigated was to find the optimum time for efficient diazo transfer. It was decided to use 5h reaction time, and compare the conversions obtained after this time period to those obtained when an overnight reaction time is used – these results are summarised in **Table 2.21**.

Table 2.21 ***Ethyl acetoacetate under various reaction conditions***



9 **11**

Entry	*Solvent*	*Volume*	*Concentration*	*Time*	*Base Loading*	*Conversion* [1]
1	H_2O	1.5 mL	0.56 mol/L	19h	5 mol%	94%
2	H_2O	1.5 mL	0.57 mol/L	19h	15 mol%	96%
3	CH_3CN	1.5 mL	0.59 mol/L	19h	5 mol%	98%
4	CH_3CN	1.5 mL	0.53 mol/L	19h	15 mol%	100%
5	H_2O	1.5 mL	0.57 mol/L	5h	5 mol%	92%[2]
6	H_2O	1.5 mL	0.56 mol/L	5h	15 mol%	92%[2]
7	CH_3CN	1.5 mL	0.55 mol/L	5h	5 mol%	98%
8	CH_3CN	1.5 mL	0.55 mol/L	5h	15 mol%	100%

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

[2] 100% of starting material consumed. Unknown impurity with ethyl peaks at 1.4 ppm (t) and 4.4 ppm (q). Impurity not recovered following column chromatography on silica gel.

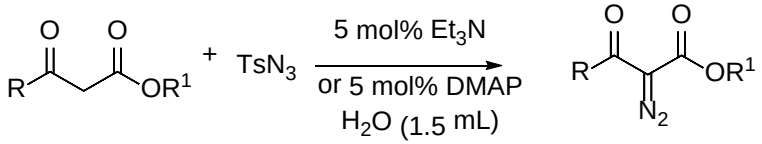
It is interesting to note that there is very little difference observed in the conversions obtained after 5 h when compared to those obtained under the same reaction conditions using longer reaction times. This is interesting to note, as it appears that, for this substrate, the reaction is effectively complete after a short period of time, with the longer reaction time only increasing conversion by ~5%, particularly when acetonitrile is used with the increased base loading of 15 mol% (**Table 2.21**, Entry 8).

2.3.6 Diazo transfer in water using 5 mol% of base – substrate scope

The next step in the development of this 'greener' diazo transfer methodology is to apply the findings to date to a wider range of substrates. The β-ketoesters prepared in **Section 2.2.1** were used to apply our new methodology. All reactions were carried out at room temperature and under an inert atmosphere, the results of which are outlined in **Table 2.22** below. The average concentration for these reactions was ~0.16 mol/L (1.5 mL solvent).

These reactions were monitored by TLC to indicate reaction completion. Interestingly, overnight reaction times of 16-18h were required in all cases for these substrates. As can be seen from **Table 2.22** below, excellent conversions to the desired product were achieved in all cases, using 5 mol% of either triethylamine or DMAP in water. There is no clear difference in conversion between the two bases. A mixture of short and long chain esters were chosen, as well as using an *n*-propyl ketone side chain in **15** and the methodology proved effective in all cases. It had been envisioned that the longer, more lipophilic chains of **17** and **18** would prove problematic when the reaction was carried out in water but this was not the case.

Table 2.22 ***Expansion of substrate scope***



Entry	*R*	*R[1]*	*Diazo Product*	*Base (5 mol%)*	*% Conversion[1]*	*% Yield after KOH wash [2]*	*% Purity*	*% Yield [3]*
1	Me	*t*-Butyl	**12**	Et_3N	99	81	90	51
2	Me	*t*-Butyl	**12**	DMAP	95	80	87	50
3	Me	Pentyl	**13**	Et_3N	98	94	95	60
4	Me	Pentyl	**13**	DMAP	98	88	89	62
5	Me	2-Ethylbutyl	**16**	Et_3N	100	73	80	50
6	Me	2-Ethylbutyl	**16**	DMAP	98	86	95	58
7	Me	3,7-dimethyloct-6-enyl	**18**	Et_3N	93	82	88	52
8	Me	3,7-dimethyloct-6-enyl	**18**	DMAP	93	79	93	54
9	Me	Undec-10-en-1-yl	**17**	Et_3N	91	92	73	66
10	Me	Undec-10-en-1-yl	**17**	DMAP	91	86	91	60
11	*n*-Propyl	Et	**15**	Et_3N	84	89	88	61
12	*n*-Propyl	Et	**15**	DMAP	93	88	90	64

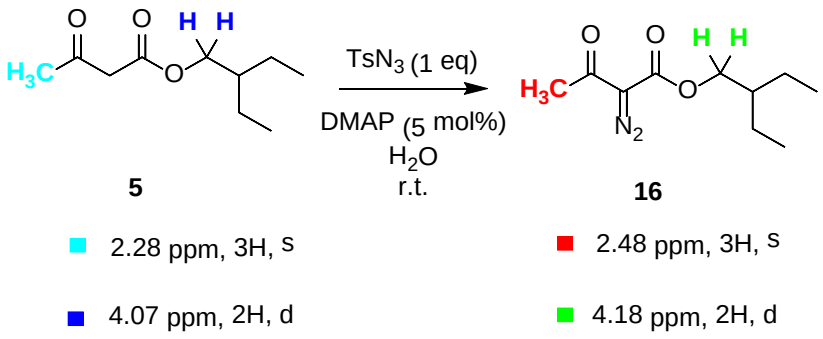
[1] % Conversion calculated from appropriate peak with key signal change in the ^1H NMR spectrum between starting material and product. **[2]** This yield reflects a synthetically pure sample. The % purity is reported in the following column. A ^1H NMR spectrum was obtained after the reaction mixture had been re-dissolved in EtOAC, washed with 3 x 15 mL 9% KOH solution, followed by 1 x 15 mL H_2O. The EtOAc layers were then combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. **[3]** Yield of analytically pure samples that were obtained by purification using column chromatography on silica gel.

The work-up involving KOH washes outlined above in **Section 2.3.3** was employed to remove the *p*-toluenesulfonamide by-product **2** of these reactions, however was found to be less effective when the reaction was carried out in water than in organic solvents. This can be explained by the conversions to diazo product obtained, as when the reaction did not go to completion, a larger quantity of *p*-toluenesulfonyl azide **1** remains in the reaction mixture. This is not removed in the KOH wash, therefore the product obtained may be of lower purity.

When these reactions are done in acetonitrile, there is often 100% conversion to the desired product, which means that there is 100% consumption of the β-ketoester and of *p*-toluenesulfonyl azide **1**. The efficiency of these reactions when water is used as reaction solvent is slightly decreased, with average conversions of 95%. The purpose of the KOH washes in the aqueous work-up is to remove *p*-toluenesulfonamide **2**, however trace quantities of β-ketoester and *p*-toluenesulfonyl azide **1** remain in the reaction mixture following work-up, resulting in decreased purity.

Samples obtained following base washes were generally >90% pure, however if analytically pure samples were required it was necessary to carry out flash chromatography. The low yields obtained after column chromatography are explained by the close R_f values of the diazo product and the *p*-toluenesulfonamide by-product **2**, as shown in **Figure 2.7** (pg. 98).

Scheme 2.13 below shows the key ^{1}H NMR shift changes observed when diazo transfer is carried out on 2-ethylbutyl 3-oxobutanoate **5**. In addition to this, the 2H singlet at δ_H 3.46 ppm corresponding to the methylene protons in **5** is absent in the ^{1}H NMR spectrum of **16**. Entry 6 in **Table 2.22** outlines diazo transfer to 2-ethylbutyl 3-oxobutanoate **5** using 5 mol% DMAP in water, and represents the most effective use of base washes in the purification of this series of reactions, as this sample had the highest purity after work-up alone (95%).



Scheme 2.13

Figure 2.20 shows the ^{1}H NMR spectrum of **5** (a); ^{1}H NMR spectrum of the crude reaction mixture from the above reaction (b); the ^{1}H NMR spectrum of the reaction mixture following work-up (c); and the ^{1}H NMR spectrum of the product, 2-ethylbutyl 2-diazo-3-oxobutanoate **16**, following column chromatography (d). As can be seen from the second spectrum, conversion to diazo product is very high at 98%, with only trace amounts of the starting ester **5** visible. This conversion was judged by the ratio of the singlet at δ_H 2.28 ppm, corresponding to **5**, and the singlet at δ_H 2.48 ppm, corresponding to **16**, as highlighted below. Two sets of aromatic signals are visible in the region from δ_H 7-8 ppm, corresponding to the aromatic rings of *p*-toluenesulfonyl azide **1** and *p*-toluenesulfonamide **2**.

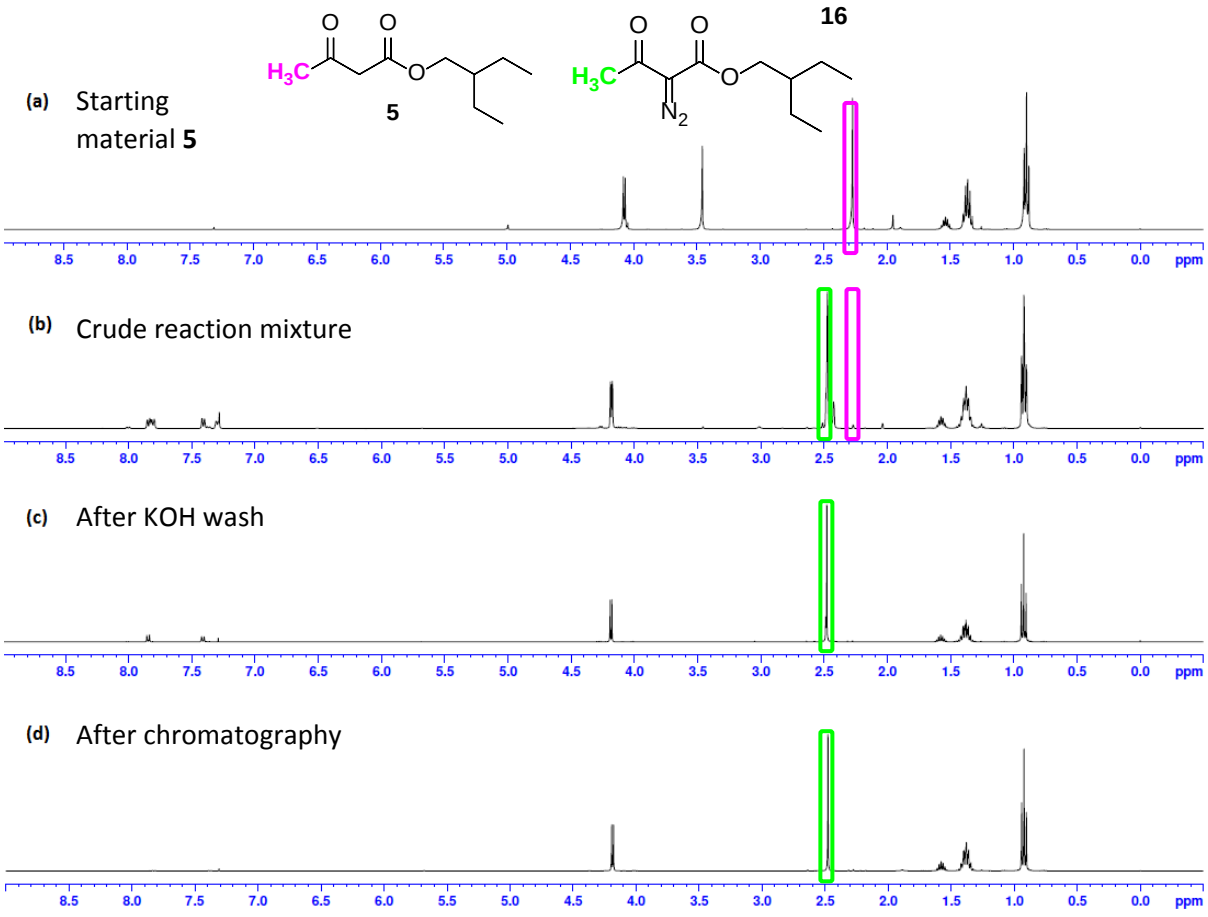
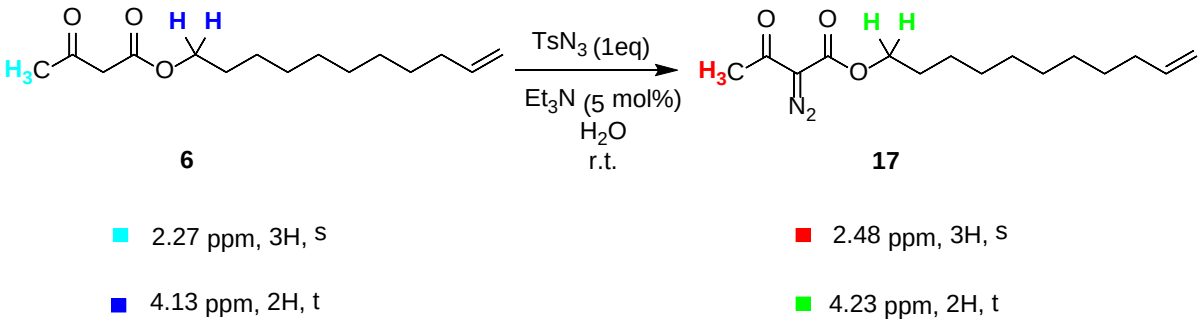


Figure 2.20 ^{1}H NMR spectra of the crude reaction mixtures of the following reactions: (a) 1 eq. 2-ethylbutyl 3-oxobutanoate **5** with 1 eq. *p*-toluenesulfonyl azide and 5 mol% DMAP in 1.5 mL water crude reaction mixture, (b) Crude reaction mixture after work-up with KOH washes, (c) Pure 2-ethylbutyl 2-diazo-3-oxobutanoate **16** following column chromatography.

Spectrum (c) in **Figure 2.20** shows the ^{1}H NMR spectrum of the reaction mixture following work-up with base washes. As can be seen, the spectrum is significantly cleaner, with no trace of **5**, and one set of aromatic signals belonging to the sulfonamide **2** has been removed completely. Samples were synthetically useful for further reactions after KOH wash only. A trace amount of unreacted p-toluenesulfonyl azide remains in the sample, ~5% by ^{1}H NMR, therefore **16** was isolated in 95% purity and 86% yield following purification by work-up. In order to obtain analytically pure samples, flash chromatography on silica gel is employed and **16** is obtained in 58% yield (Spectrum (d), **Figure 2.20**).

This moderate yield is explained by the problematic separation of the product **5** and *p*-toluenesulfonyl azide **1**, which have very similar R_f values in all solvent systems screened for their separation. This means that **1** trails off with the desired product over a number of test tubes. Only 100% pure test tubes were collected, as for the purpose of the publication included later in this thesis, very clean spectra were required for these samples. Further chromatography of the test tubes which contained small quantities of **1** along with the product could lead to much higher yields.

Unfortunately the KOH wash was not so successful in all cases. Entry 9 in **Table 2.22** above shows the outcome when diazo transfer to undec-10-en-1-yl 3-oxobutanoate **6** is attempted in water using 5 mol% triethylamine as base (**Scheme 2.14**).



Scheme 2.14

Figure 2.21 shows the ^{1}H NMR spectrum of the crude reaction mixture (a), the ^{1}H NMR spectrum of the reaction mixture following work-up (b), and the ^{1}H NMR spectrum of the product, undec-10-en-1-yl 2-diazo-3-oxobutanoate **17**, following column chromatography (c). 91% conversion of the **6** to **17** was achieved under these reaction conditions, which was judged from the ratio of the 2H triplet of **6** at δ_H 4.13 ppm to the 2H triplet of **17** at δ_H 4.23 ppm. As can be seen clearly in the expansion, a third triplet corresponding to an unknown impurity is evident at δ_H 4.32 ppm.

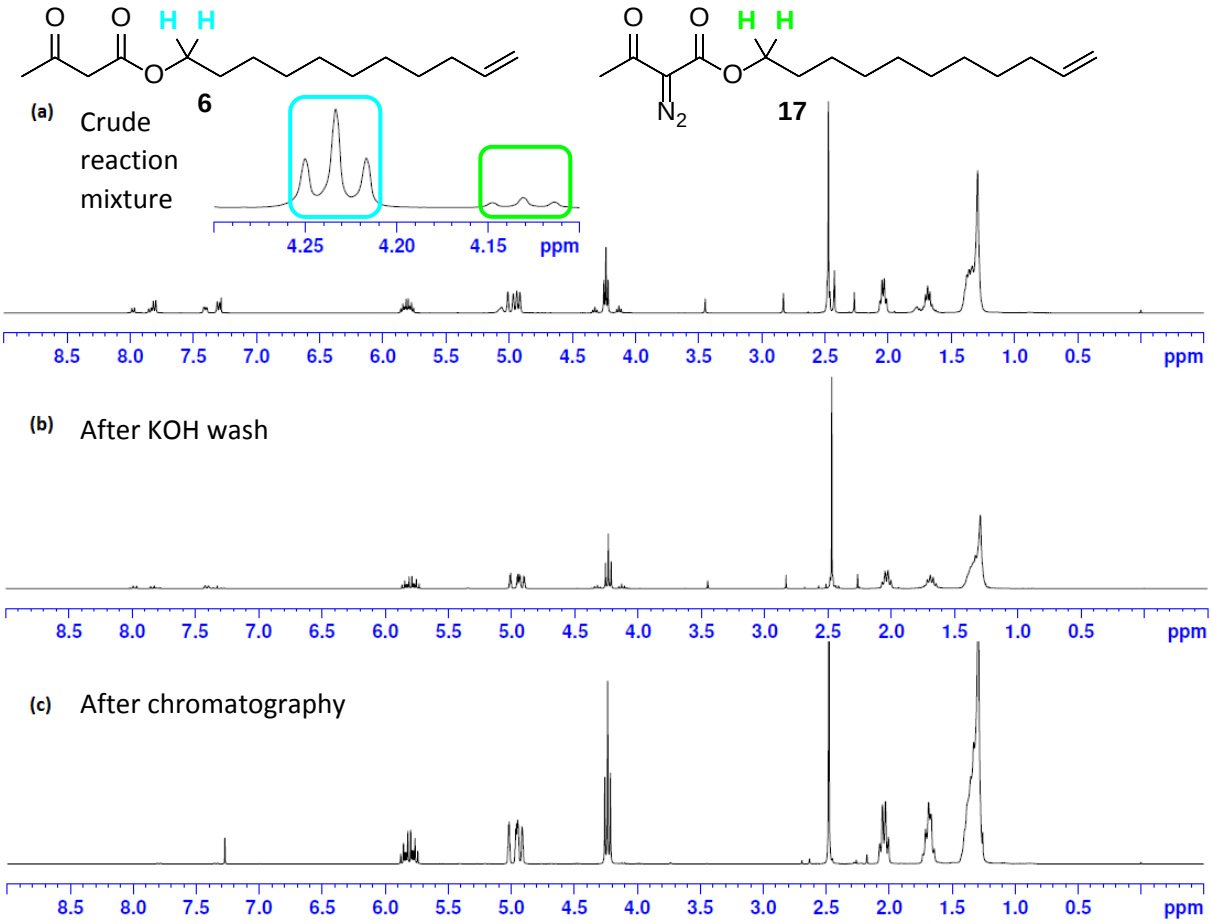


Figure 2.21 ^{1}H NMR spectra of the crude reaction mixtures of the following reactions: (a) 1 eq. undec-10-en-1-yl 3-oxobutanoate **6** with 1 eq. *p*-toluenesulfonyl azide and 5 mol% DMAP in 1.5 mL water crude reaction mixture, (b) Crude reaction mixture after work-up with KOH washes, (c) Pure undec-10-en-1-yl 2-diazo-3-oxobutanoate **17** following column chromatography.

Following an aqueous work-up with KOH washes, spectrum (b) in **Figure 2.21** was obtained. As can be seen below, in this instance the work-up removed much of the p-

toluenesulfonamide by-product **2** but did not remove the unreacted starting material, or unknown impurity at δ_H 4.32 ppm. This resulted in undec-10-en-1-yl 2-diazo-3-oxobutanoate **17** being isolated in 92% yield, but only 73% purity. Following purification on silica gel, undec-10-en-1-yl 2-diazo-3-oxobutanoate **17** was obtained in 66% yield and 100% purity, shown below in spectrum (c).

Overall, diazo transfer was achieved in the most environmentally friendly solvent, water, which avoids the use of chlorinated solvents or acetonitrile with no substantial decrease in conversion to diazo product. In addition the safety improvement is enormous - using non-flammable water as the reaction solvent is very attractive from an industrial large scale viewpoint. In addition to this, diazo transfer with a catalytic amount of base has been shown to be effective across a range of long and short chain β-ketoesters with no substantial reduction in conversion to the desired product. This is in contrast to the well-established protocols where it is accepted that at least one equivalent of base is required for these β-ketoester systems, and in keeping with the 12 Principles of Green Chemistry as outlined by Anastas.[13]

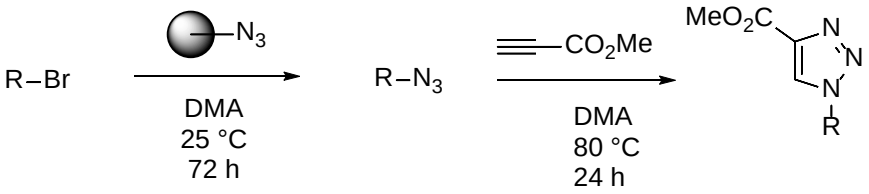
2.4 Diazo transfer using polymer-supported azide

2.4.1 Background

At this stage, our new methodology used an environmentally benign solvent, with a reduced loading of base, however due to the safety concerns associated with the use of *p*-toluenesulfonyl azide **1** this method is unlikely to be used on an industrial scale without inclusion of a diazo transfer reagent which has an improved safety profile. Also the use of **1** means that chromatography is necessary to purify the samples obtained, which has been shown to compromise the yields.

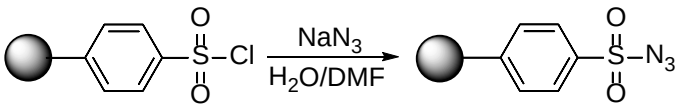
2.4.2 Synthesis of polystyrene-supported benzenesulfonyl azide

Hassner and Stern reported the first polymer-supported azide as an azide ion exchange reagent in nucleophilic substitution reactions to form alkyl azides.[29] Blass and co-workers later used this reagent, along with another polymer-supported azide of their own design in a one-pot synthesis of 1,2,3-triazoles, as shown in **Scheme 2.15**.[30]



Scheme 2.15

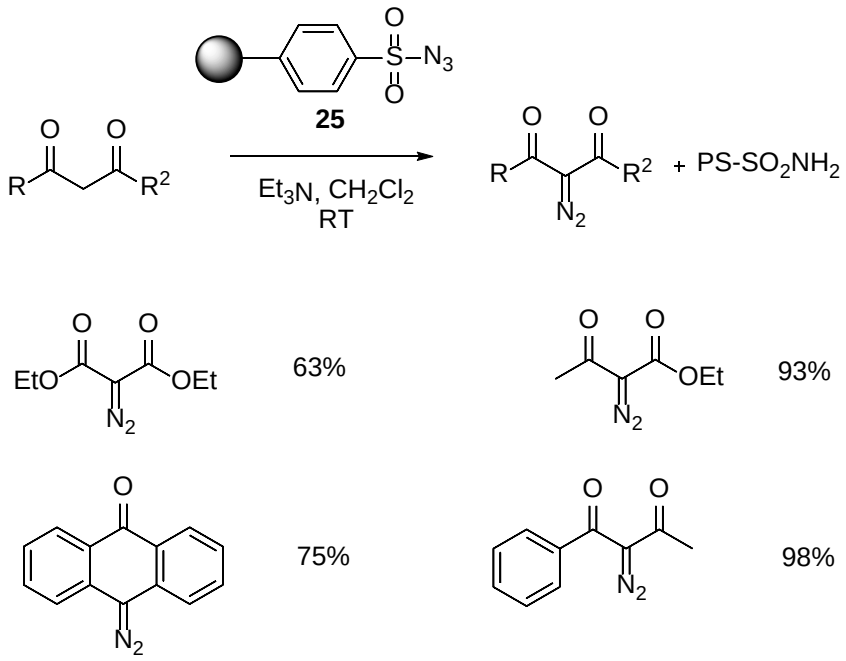
Green and co-workers reported the first use of polystyrene-supported benzenesulfonyl azide **25** as a diazo transfer reagent that is both efficient and safe.[8] This may be prepared by treatment of the corresponding commercially-available polymer-supported benzenesulfonyl chloride **26** with sodium azide (**Scheme 2.16**), and has several benefits compared to *p*-toluenesulfonyl azide **1**. These include significantly thermal stability, ease of handling, improved safety profile, as well as ease of purification of the diazocarbonyl product – no KOH wash is required as the polymer-supported benzenesulfonyl amide by-product **27** can be removed by filtration.



26 **25**

Scheme 2.16

The authors successfully used polystyrene-supported benzenesulfonyl azide **25** to achieve diazo transfer to a range of substrates including β-ketoesters and diketones in good to excellent yields (**Scheme 2.17**).



Scheme 2.17

It was anticipated that this reagent might solve the remaining issues with our methodology; the improved safety profile and thermal stability associated with **25** without loss of reactivity allowed a move away from *p*-toluenesulfonyl azide **1**. In addition to this, isolation of the α-diazocarbonyl product by simple filtration of the polymer is vastly more appealing than an aqueous work-up, followed by column-chromatography, especially from an industry perspective.

With this is mind, polystyrene-supported benzenesulfonyl azide **25** was successfully prepared using the method outlined by Green and co-workers. The presence of the azide functionality was confirmed by FTIR, which showed the appearance of a strong band at 2125 cm^{-1}, as shown below in **Figure 2.22**.

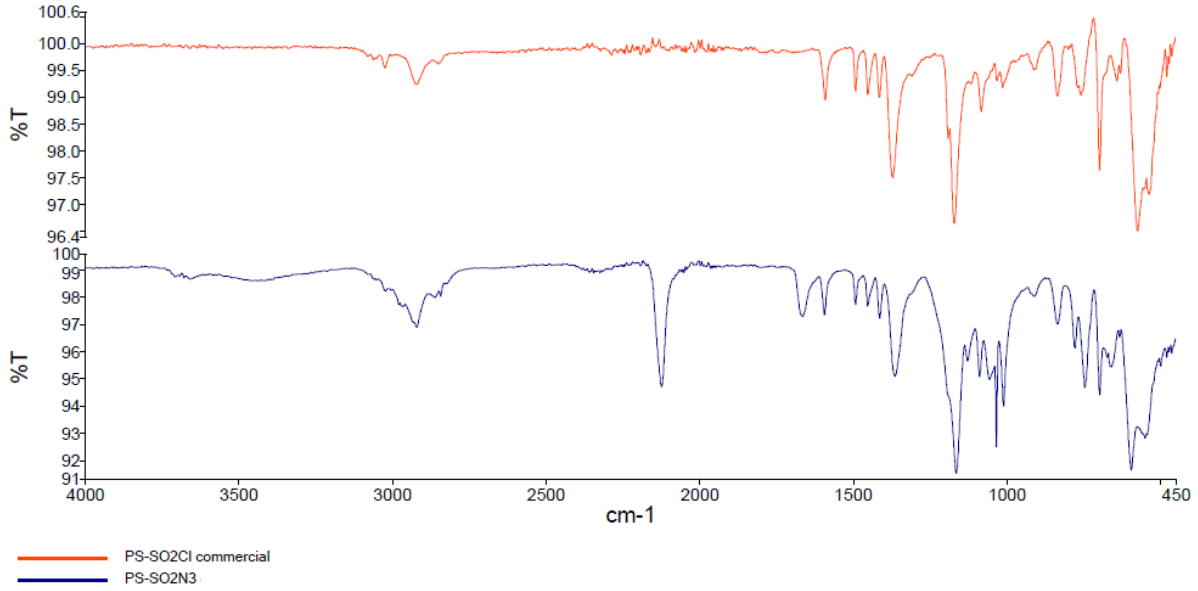
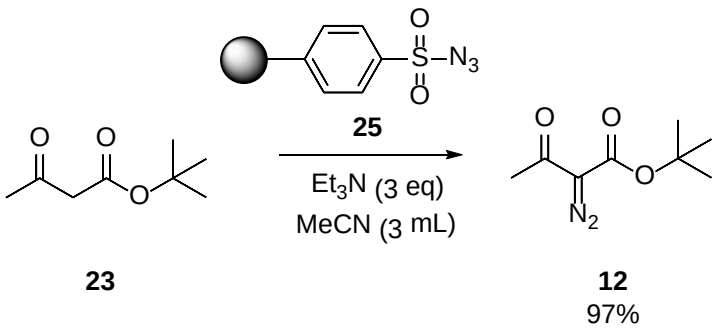


Figure 2.22 IR spectrum of commercially available polymer-supported benzenesulfonyl chloride; IR spectrum of polymer-supported benzenesulfonyl azide synthesised as shown in Scheme 2.16 (pg 128).

2.4.3 Diazo transfer reactions using polystyrene-supported benzenesulfonyl azide – substrate scope

Although Green and co-workers carried out successful diazo transfer with polystyrene-supported benzenesulfonyl azide **25** in dichloromethane, previous work within the group showed the reagent could also be employed effectively in acetonitrile, as shown in **Scheme 2.18**.[14]



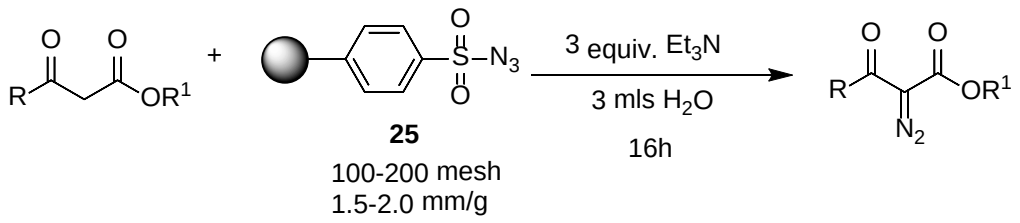
Scheme 2.18

Preliminary work was also carried out by Tarrant using **25** in water.[14] Therefore it was decided to expand on the previous work within the group by carrying out a much more detailed study. The aim of this part of the project was to attempt to optimise a greener diazo transfer methodology with **25** in water with different base loadings, and to subsequently carry out diazo transfer using polystyrene-supported benzenesulfonyl azide **25** in water, using the range of β-ketoesters synthesised in **Section 2.2.1**.

It should be noted that when the reaction is carried out in water instead of an organic solvent, modification of the procedure outlined in Green's paper is required.[8] In dichloromethane, filtration of the polymer-supported benzenesulfonyl amide **27**, followed by concentration of the reaction mixture are the only steps required to isolate the α-diazo-β-ketoester.

However when the reaction is carried out in water, isolation of the product is carried out by filtration of the reaction mixture, and extraction of the filtrate with diethyl ether. This method successfully isolated the α-diazo-β-ketoester, but in depleted yields. Therefore, re-stirring of the filtered solid in ether for 2 h was found to desorb product which had adsorbed to the solid. Combination of the ethereal layers, followed by concentration resulted in very good yields, as shown below in **Table 2.23**.

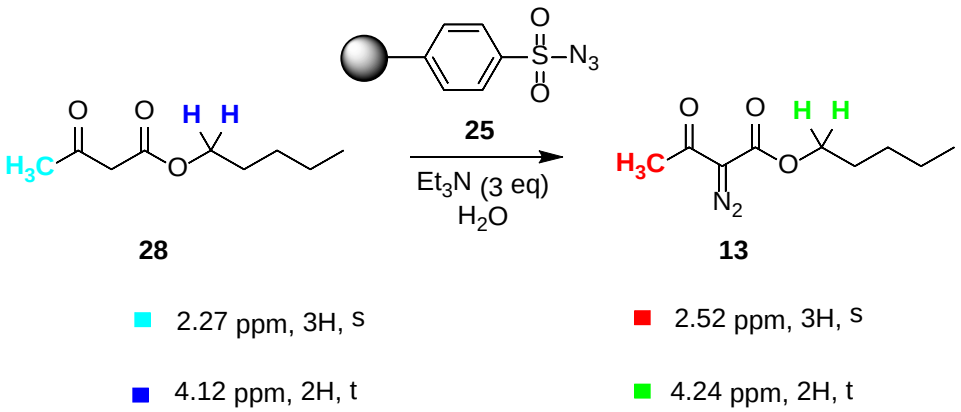
Table 2.23 ***Diazo transfer reactions using polystyrene-supported benzenesulfonyl azide***



Entry	*R*	R^1	Diazo compound	Concentration	% Conversion	% Yield
1	Me	*t*-Butyl	**12**	0.16 mol/L	100	65
2	Me	Pentyl	**13**	0.16 mol/L	100	71
3	Me	2-Ethylbutyl	**16**	0.16 mol/L	100	74
4	Me	3,7-Dimethyloct-6-enyl	**18**	0.16 mol/L	100	77
5	Me	Undec-10-en-1-yl	**17**	0.16 mol/L	100	70
6	*n*-Propyl	Et	**15**	0.16 mol/L	96[1]	70

[1] 100% of starting material consumed. Unknown impurity with peaks at 3.0 ppm (t) and 4.4 ppm (q). Quantity estimated at <5%.

As can be seen above, 100% conversion from β-ketoester to α-diazo-β-ketoester was obtained in almost all cases, with good isolated yields. As with previous examples, conversion was judged by key chemical shift changes. In the case of pentyl 3-oxobutanoate **28** (**Table 2.23**, Entry 2), the key chemical shift changes are outlined in **Scheme 2.19**. The 2H singlet at δ_H 3.45 ppm corresponding the methylene protons of pentyl 3-oxobutanoate **28** disappears following diazo transfer. It should be noted that these reactions were done using 0.5 mmol of starting ester in 3 mL of water, giving a reaction concentration of 0.16 mol/L. This achieved similar concentrations to those used in previous screens where 1.5 mL of water was used as solvent using **1** as diazo transfer reagent.



Scheme 2.19

Spectrum (a) in **Figure 2.23** below shows pentyl 3-oxobutanoate **28,** and the ^{1}H NMR of the crude reaction mixture from Entry 2 above is shown in spectrum (b). As can be seen, this is a remarkably clean reaction, with no trace of starting material remaining. Due to the use of polystyrene-supported benzenesulfonyl azide **25** the aromatic region is completely clear.

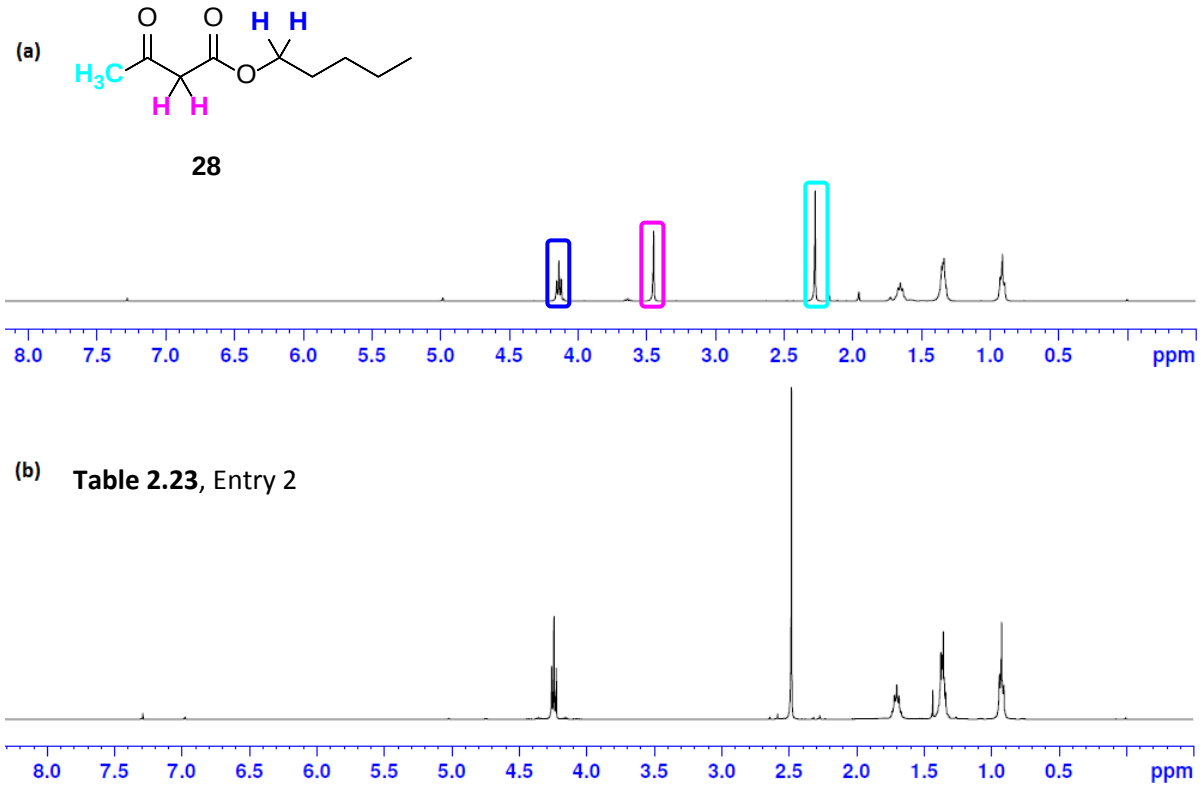
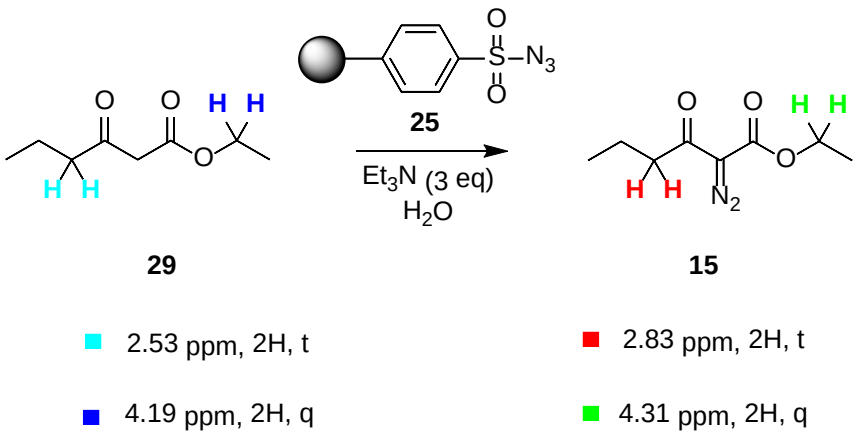


Figure 2.23 (a) Pentyl 3-oxobutanoate **28**, (b) 1 eq. pentyl 3-oxobutanoate **28** with 1.5 eq. polymer-supported benzenesulfonyl azide and 3 eq. Et_3N in 3 mL water crude reaction mixture.

Interestingly, when ethyl 3-oxohexanoate **29** was used as starting material, a trace amount of an unknown impurity was observed in the ^{1}H NMR spectrum of the crude reaction mixture. A triplet is seen at δ_H 3.0 ppm and a quartet at δ_H 4.4 ppm, which do not correspond to either ethyl 3-oxohexanoate **29** or ethyl 2-diazo-3-oxohexanoate **15** (**Scheme 2.20**).



Scheme 2.20

It is possible that these signals correspond to a similar impurity which has been observed previously, shown in **Figure 2.14** (pg 109). The tentative structure for this impurity is shown below in **Figure 2.24**. When this impurity has been formed in earlier examples, it has not been isolated following column chromatography.

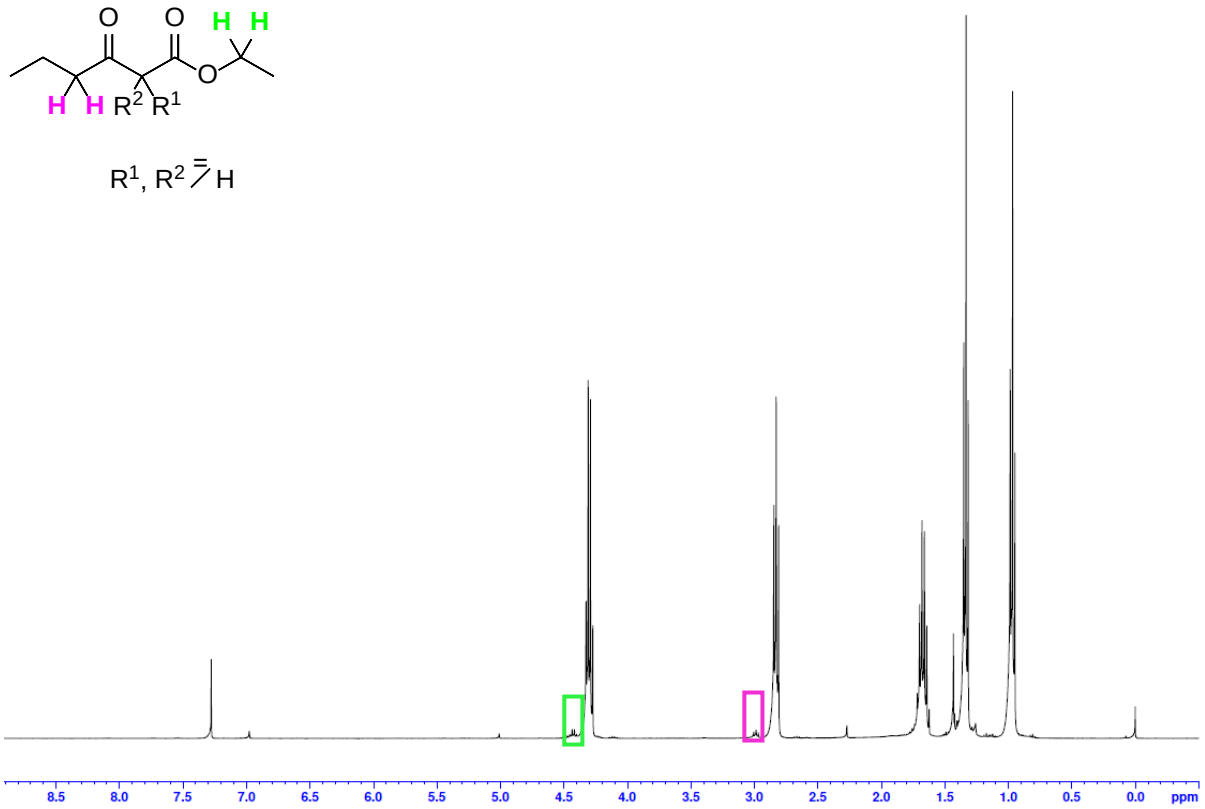
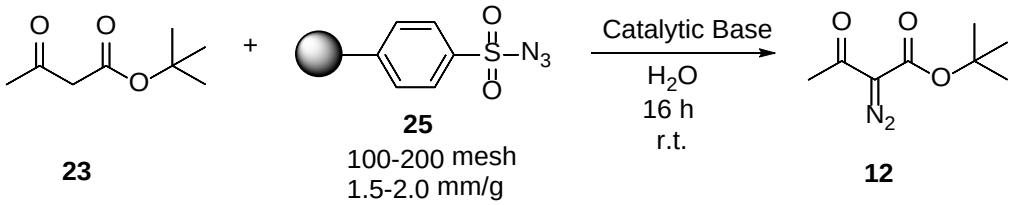


Figure 2.24 ^{1}H NMR spectrum of the crude reaction mixture of **Table 2.22**, Entry 6.

2.4.4 Diazo transfer reactions using polystyrene-supported benzenesulfonyl azide and catalytic base loading

Although the results obtained with the polymer-bound benzenesulfonyl azide **25** and three equivalents of base above are very positive, a key goal in this investigation was to see if a base-catalysed diazo transfer using the polymer bound reagent in water could be achieved. With this in mind, several attempts were made to attain diazo transfer using the procedure outlined above, but with 5 mol% of base. Unfortunately, only trace amounts of the diazo product were observed when this method was used. Therefore, a screen was undertaken with reactions carried out using base loadings of 0.18, 0.20 and 0.25 equivalents of trimethylamine and DMAP. The results are outlined below (**Tables 2.24 and 2.25**). *t*-Butyl acetoacetate **23** and ethyl 3-oxohexanoate **29** were chosen for this study.

Table 2.24 ***Polystyrene-supported benzenesulfonyl azide with catalytic base***



23 **25** 100-200 mesh 1.5-2.0 mm/g **12**

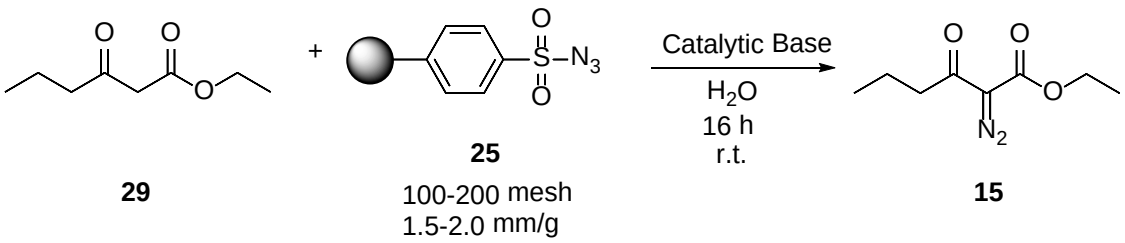
		Base Loading		
Base	Diazo Product	18 mol%	20 mol%	25 mol%
DMAP	**12**	74	95	36
Et_3N	**12**	91	97	94

Table shows % conversions.

As can be seen above in **Table 2.24**, in all cases, excellent conversions from *t*-butyl acetoacetate **23** to *t*-butyl 2-diazo-3-oxobutanoate **12** were obtained when triethylamine was utilised as base at various sub-stoichiometric quantities. However when DMAP was employed, a drop-off in conversion was observed when the base loading was increased from 20 mol% to 25 mol%.

When the same screen was carried out on ethyl 3-oxohexanoate **29**, inconsistent results with DMAP were observed, as can be seen in **Table 2.25**. These unusual results with DMAP are perhaps explained by the solid state of the reagent – when a solvent volume of only 3 mL is used, a large amount of the solvent is used in 'swelling' of the polymer-bound benzenesulfonyl azide **25** prior to addition of the ester and base, therefore the effective solvent volume is significantly less. This could result in poor mixing of the solid DMAP with the ester in the presence of **25**. Due to the unreliable results obtained with DMAP in these reactions it was decided to discontinue its use in the course of these reactions.

Table 2.25 ***Polystyrene-supported benzenesulfonyl azide with catalytic base***



29 **25** 100-200 mesh 1.5-2.0 mm/g **15**

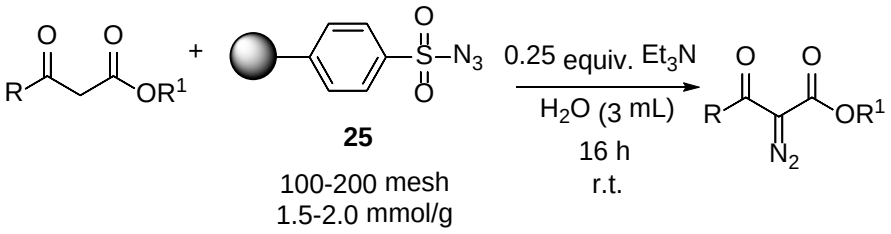
		Base Loading		
Base	Diazo Product	18 mol%	20 mol%	25 mol%
DMAP	**15**	70	33	61
Et_3N	**15**	32	83	91

Table shows % conversions.

In the cases of both *t*-butyl acetoacetate **23** and ethyl 3-oxohexanoate **29,** triethylamine gave excellent conversions when 20 mol% or 25 mol% loading was used. Therefore it was decided to proceed using 25 mol% of triethylamine as the optimum base loading required to furnish the best conversions for these reactions. Although this is somewhat high loading for a catalytic reagent, it is is a substantial reduction from three equivalents used for these reactions up until this point.

When these reaction conditions were employed with a range of β-ketoesters excellent conversions were obtained for shorter chain esters, as can be seen in **Table 2.26**. Unfortunately, in the case of esters with longer, more lipophilic side-chains a reduced conversion is observed.

Table 2.26 ***Polystyrene-supported benzenesulfonyl azide with catalytic base – substrate scope***

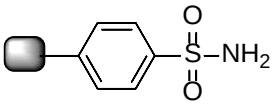


Entry	*R*	*R[1]*	*Diazo product*	*Conversion (%)*
1	Me	*t*-Butyl	**12**	94
2	Me	Pentyl	**13**	97
3	Me	2-Ethylbutyl	**16**	94
4	Me	3,7-dimethyloct-6-enyl	**18**	65
5	Me	Undec-10-en-1-yl	**17**	69
6	*n*-Propyl	Et	**15**	91

2.5 Synthesis of polymer-supported benzenesulfonyl azide

2.5.1 Background

Although using a polystyrene-supported benzenesulfonyl azide **25** has several advantages over the traditional *p*-toluenesulfonyl azide **1**, it has one major disadvantage in that it is cost prohibitive at €77 for 5 g of polymer-supported benzenesulfonyl chloride **26**. Were this reagent to be used as a safe means to prepare α-diazocarbonyl compounds on an industrial scale, this issue would have to be addressed in one of two ways; recycling of the polymer-supported benzenesulfonyl amide side product **27**, or use of a more affordable starting material.



27

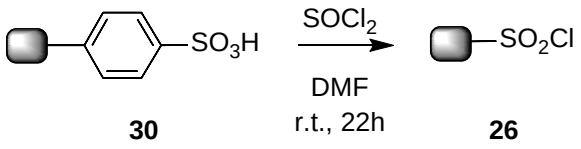
Figure 2.25

Recycling of the polymer-supported benzenesulfonyl amide side product **27** would be the ideal solution to this problem, as it would serve the dual role of reducing costs and of further reducing the environmental impact of this reaction – Anastas and Warner cited 'use of renewable feedstocks' as one of their 12 Principles of Green Chemistry.[13] Several attempts have been made within our group to date to recycle this polymer side product, either by conversion of the amide to the chloride, or by direct conversion to the azide, however these have all been unsuccessful to date.

With this in mind, it was decided to attempt to find a more economical synthesis of polystyrene-supported benzenesulfonyl azide **25** *via* synthesis of polymer-supported benzenesulfonyl chloride **26**.

2.5.2 1st generation synthesis of polymer-supported benzenesulfonyl azide

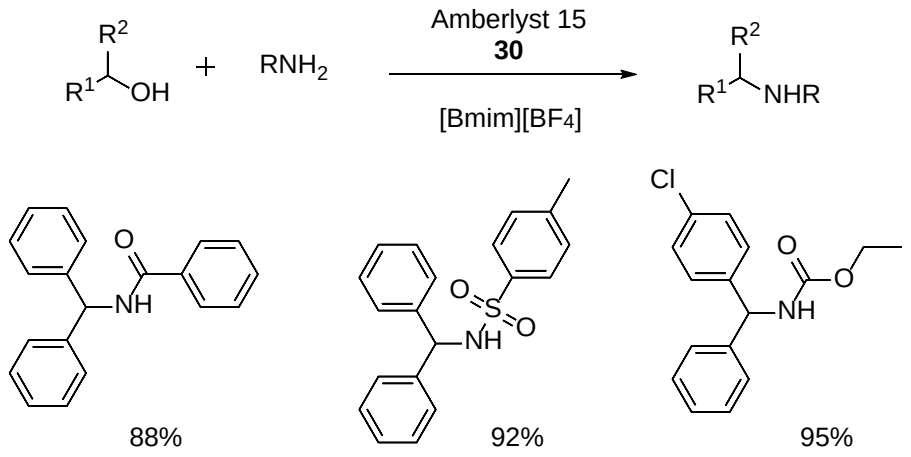
Several approaches were considered for the synthesis of polymer-supported benzenesulfonyl chloride **26**, however the best choice appeared to be conversion of a polymer-supported sulfonic acid to its corresponding chloride by reaction with thionyl chloride, as shown in **Scheme 2.21**.



Scheme 2.21

Amberlyst® 15 **30** is a macro reticular polystyrene based ion exchange resin with strongly acidic sulfonic group. Although marketed as an ion-exchange resin which may also be used as a column packing material for HPLC analysis, there are several reports in the literature of its use of a reagent in organic synthesis.[31–33] Qureshi and co-workers have described the use of Amberlyst® 15 **30** as an efficient and recyclable reagent for nucleophilic substitution of alcohols and hydroamination of alkenes (**Scheme 2.22**).[34] The authors report Amberlyst® 15

30 as the most efficient solid acid reagent tested, and credit its physical properties, such as H^+ capacity (4.2 meq/g) and high surface area (42 m^2/g) for its high reactivity.



Scheme 2.22

Amberlyst® 15 **30** was reacted with a large excess of thionyl chloride to form polymer-supported benzenesulfonyl chloride **26.** It should be noted that when this synthesis of polymer-supported benzenesulfonyl chloride **26** was scaled up, large amounts of a yellow/brown powder by-product remained with the beads when they were isolated by filtration. Small amounts of this powder impurity had been observed when the reaction had been carried out at a lower scale, but this small quantity had been removed by washing the beads several times with dichloromethane. When this method proved unsuccessful for larger quantities of the impurity, solubility tests were carried out on the powder, and it was found to be soluble in hot acetonitrile.

The mixture of polymer-supported benzenesulfonyl chloride **26** and the powder impurity was placed in an Omnifit glass column, where a pump was used to pass acetonitrile through the sample at 70° C at a rate of 2.5 mL/min. This method was successfully used to purify the remaining polymer-supported benzenesulfonyl chloride **26**.

Polymer-supported benzenesulfonyl chloride **26** was then reacted with sodium azide to form polystyrene-supported benzenesulfonyl azide **25**. As can be seen from the IR spectra below

in **Figure 2.25**, there is an appearance of a weak band at 2136 cm^{-1} following reaction with sodium azide. Although this band is weak, it is confirmation that some polystyrene-supported benzenesulfonyl azide **25** is being formed.

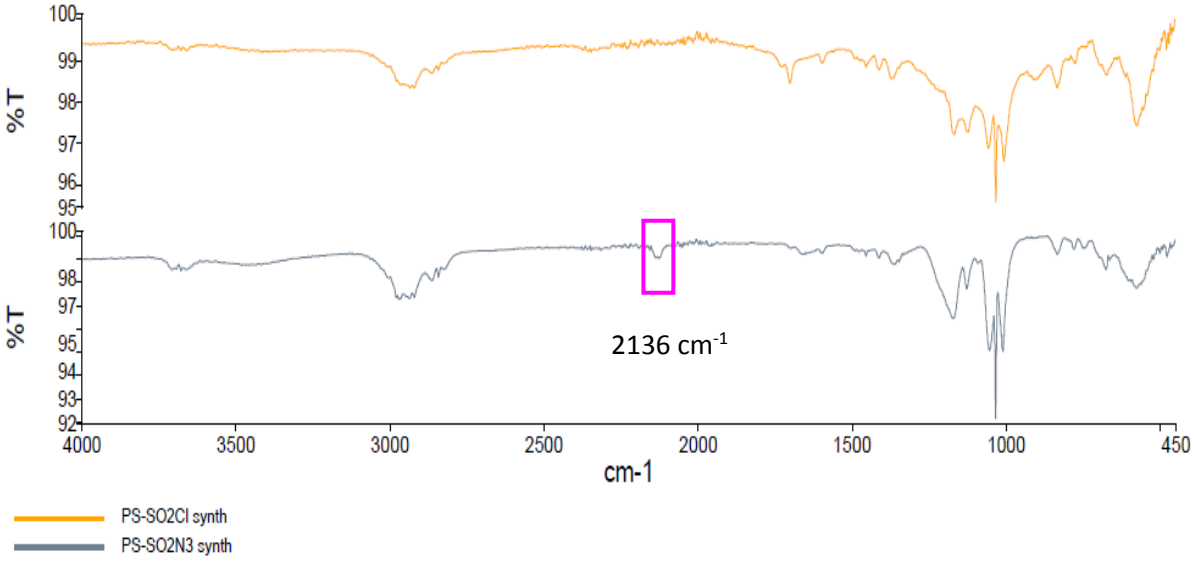
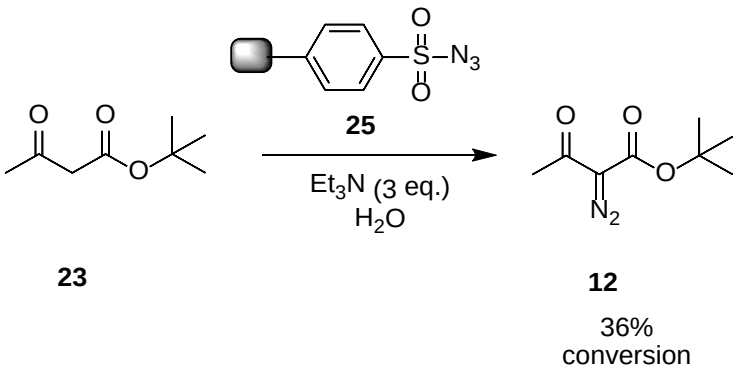


Figure 2.26 IR spectra of polymer-supported benzenesulfonyl chloride and azide synthesised using 1st generation synthesis

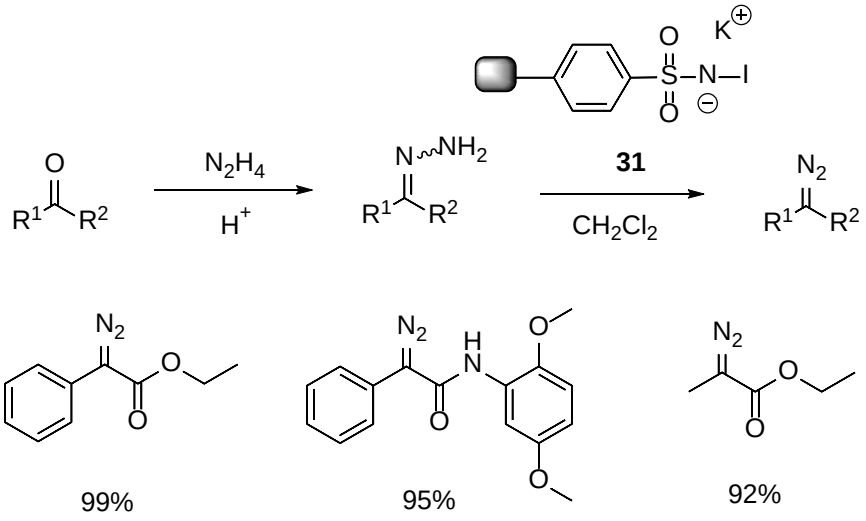
Polystyrene-supported benzenesulfonyl azide **25** was tested in a diazo transfer reaction with *t*-butyl acetoacetate **23** (**Scheme 2.23**), using conditions optimised previously in **Section 2.4.3**. Unfortunately, only 36% conversion to *t*-butyl 2-diazo-3-oxobutanoate **23** was observed by the ^{1}H NMR spectrum of the crude reaction mixture, as well as singlets at 1.48 ppm and 2.38 ppm corresponding to unknown impurities. This is likely indicative that the polymer bound reagent was a mixture of either sulfonic acid or chloride that had not been reacted adequately to form the azide. Therefore, due to the poor reactivity of this polymer **25** as well as the problems experienced during its large scale preparation, it was decided to re-evaluate the route to synthesise polystyrene-supported benzenesulfonyl azide **25**.



Scheme 2.23

2.5.3 2nd generation synthesis of polymer-supported benzenesulfonyl azide

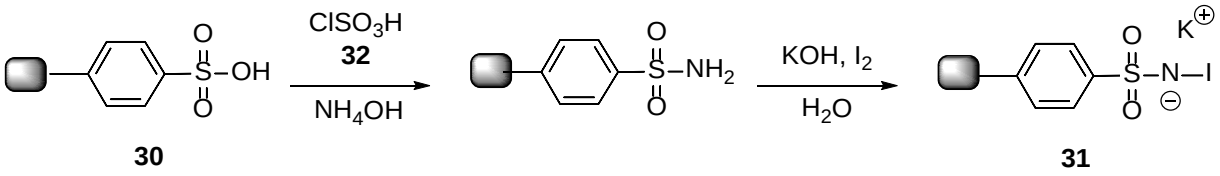
At this time, Moody and co-workers reported the use of a recyclable polymer-supported *N*-iodosulfonamide oxidant **31** for the preparation of diazo compounds using continuous processing.[35] This was achieved by conversion of ketones to hydrazones, followed by subsequent oxidation to diazo compounds, as shown in **Scheme 2.24**.



Scheme 2.24

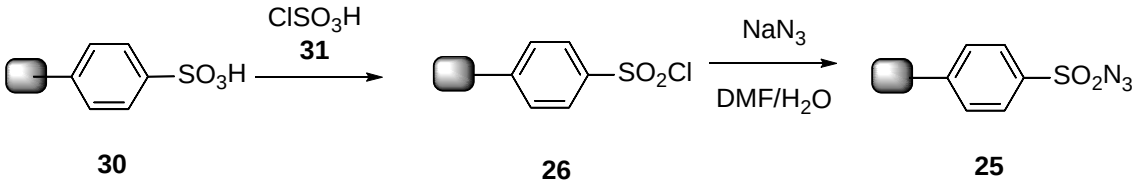
Due to the fact that this reaction was being carried out using continuous flow, it was desirable to use an immobilised oxidising agent to facilitate facile reaction clean-up downstream in the process, a concept which will be further discussed in Chapter 3. To this end, the authors

developed a polystyrene-supported iodine-based oxidising reagent **31** (**Scheme 2.25**). This reagent was developed from Amberlyst® 15 **30** *via* chlorosulfonic acid **32**, a reaction previously reported by Emerson *et al*.[36]



Scheme 2.25

The first step of Emerson's synthesis involved converting a polymer-supported sulfonic acid **30** to the corresponding polymer-supported sulfonyl chloride **26**, which was then subsequently converted to the polymer-supported sulfonyl amide **27**. It was decided to attempt the first step of this method to synthesise polymer-supported benzenesulfonyl chloride **26**, which would hopefully avoid the problem encountered previously with thionyl chloride, where large quantities of an unknown solid were seen to form in the reaction mixture. This reaction, shown below in **Scheme 2.26**, proved to be a cleaner reaction, with no visible side products, and proceeded in only 1h at reflux according to the literature procedure,[35] compared to the overnight reaction time when thionyl chloride was used for the transformation.



Scheme 2.26

The polymer-supported benzenesulfonyl chloride **26** synthesised was then subjected to sodium azide to produce polystyrene-supported benzenesulfonyl azide **25** (**Scheme 2.26**). When the IR spectra of this azide, and the azide prepared by the previous method are compared in **Figure 2.26** below, the azide absorption is seen to be much stronger in the sample prepared using chlorosulfonic acid methodology.

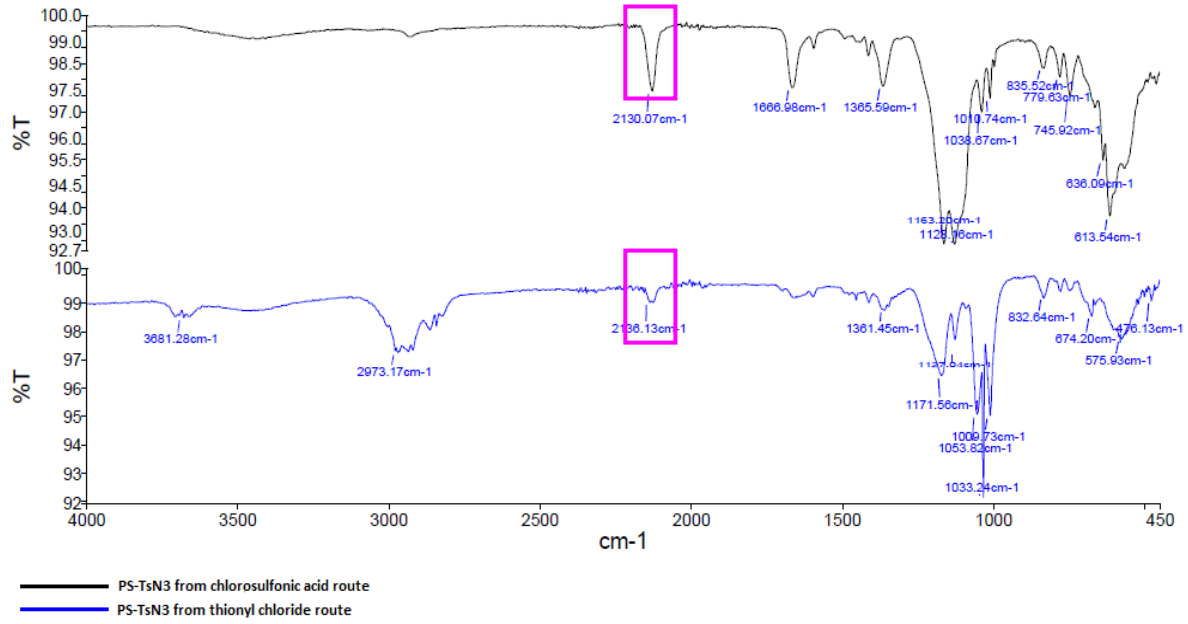


Figure 2.27 IR spectra of polymer-supported benzenesulfonyl azide from the 2nd generation synthesis and azide synthesised using 1st generation synthesis

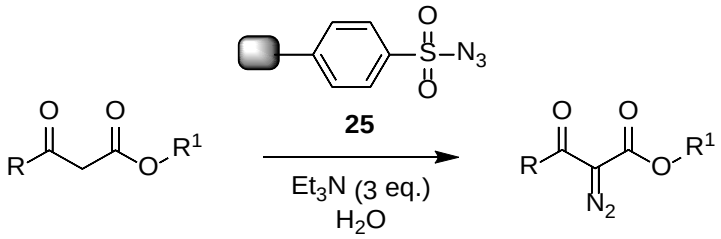
Microanalysis was also carried out on this new polymer at each stage of the reaction. These results are seen below in **Table 2.27**. As can be seen, the microanalysis confirms an increased level of chlorine present in the sample of **26** when compared to **30**. An increased level of nitrogen is also seen when **25** is compared to the other polymers. Although these results are not conclusive and cannot be used to quantitatively calculate the degree of diazotization on the surface of the polymer, they are a positive indication that the reaction was successful.

Table 2.27 ***Microanalysis results of polymers***

Substrate		***%C***	***%H***	***%N***	***%Cl***
Amberlyst® 15	**30**	50.02	6.27	0.04	<0.3
polymer-supported benzenesulfonyl chloride	**26**	26.86	6.20	0.02	1.28
polystyrene-supported benzenesulfonyl azide	**25**	44.32	4.25	6.76	N/A

This new polymer-supported benzenesulfonyl azide **25** was used in a number of diazo transfer reactions in order to test its efficiency. **25** was first used under standard conditions, using an excess of base in water. Excellent conversions to the desired products were obtained in both cases, as shown in **Table 2.28**, however evidence for formation of the unknown impurity previously outlined in **Figure 2.24** was again observed. This impurity was not recovered following column chromatography.

Table 2.28 ***Synthesised polystyrene-supported TsN_3 with 3eq. base***

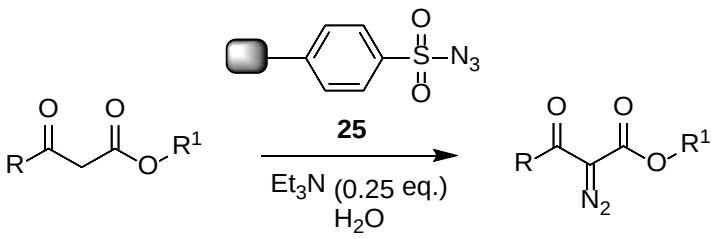


Entry	*R*	*R^1*	*Diazo product*	*Base (3 equiv)*	*Conversion (%)*
1	Me	*t*-Butyl	**12**	Et_3N	100
2	*n*-Propyl	Et	**15**	Et_3N	90[1]

[1] 100% of starting material consumed. Unknown impurity (~10%) with peaks at 3.0 ppm (t) and 4.4 ppm (q).

Unfortunately, when the new polymer was used with a catalytic quantity of base, the reactions were less successful, as seen below in **Table 2.29**. Therefore, we can conclude that although this polymer-supported benzenesulfonyl azide **25** is more active than that previously synthesised using thionyl chloride, it is less active than the polymer-supported benzenesulfonyl azide formed from the commercially available polymer-supported benzenesulfonyl chloride **26**. Therefore, further work is ongoing in the group to optimise this process.

Table 2.29 ***Synthesised polystyrene-supported TsN_3 with 0.25eq. base***



Entry	*R*	*R^1*	*Diazo product*	*Base (0.25 equiv)*	*Conversion (%)*
1	Me	*t*-Butyl	**12**	Et_3N	0
2	*n*-Propyl	Et	**15**	Et_3N	11

2.6 Mechanistic insight

As previously discussed in **Section 2.3.3**, diazo transfer has always been considered to be a stoichiometric reaction, requiring a full equivalent of base for each equivalent of the substrate. Based on the results described above, the use of a substoichiometric quantity of base to achieve quantitative diazo transfer seems to indicate that the accepted mechanism (**Scheme 2.9**, pg 90) may be more detailed than first thought. Therefore, new insights into the mechanistic pathway are required.

Bunting *et al*. carried out an extensive study into the deprotonation of β-ketoesters and amides in aqueous solution.[37] The authors reported that enolisation of β-ketoesters is promoted in water when compared to organic solvents, due to the ability of water to act as both acid and base in a concerted mechanism. Two different mechanisms by which this may occur are shown, as shown in **Figure 2.28**. In **A**, deprotonation of the methylene group by a water molecule occurs in concert with protonation of the developing enolate ion by a second water molecule to produce the neutral enol as the product.

In **B**, deprotonation by hydroxide ion is assisted by a hydroxonium ion acting as an acid to protonate the developing enolate ion. Each of the transition states below are thought to have a pre-existing complex *via* hydrogen bonding. Either of these mechanisms are supported by experimental rate and ionisation constants measured by the authors.

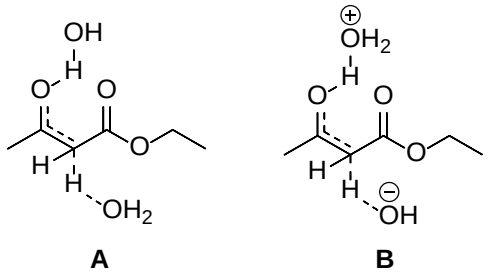
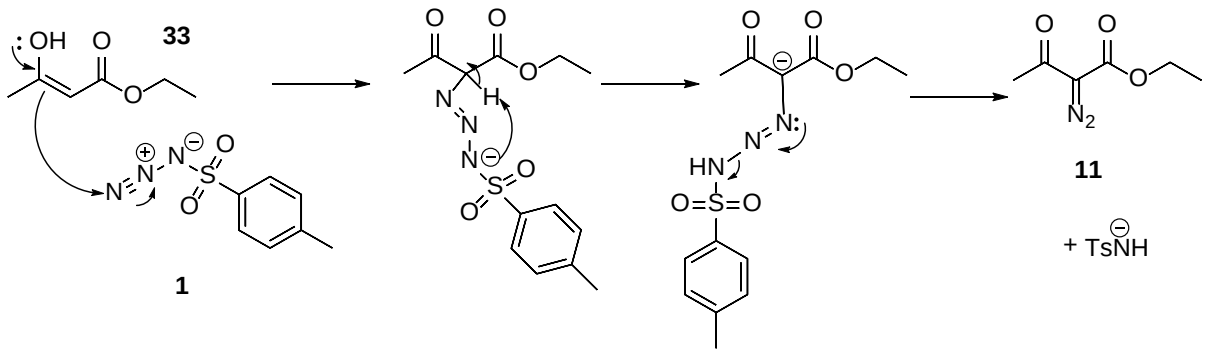


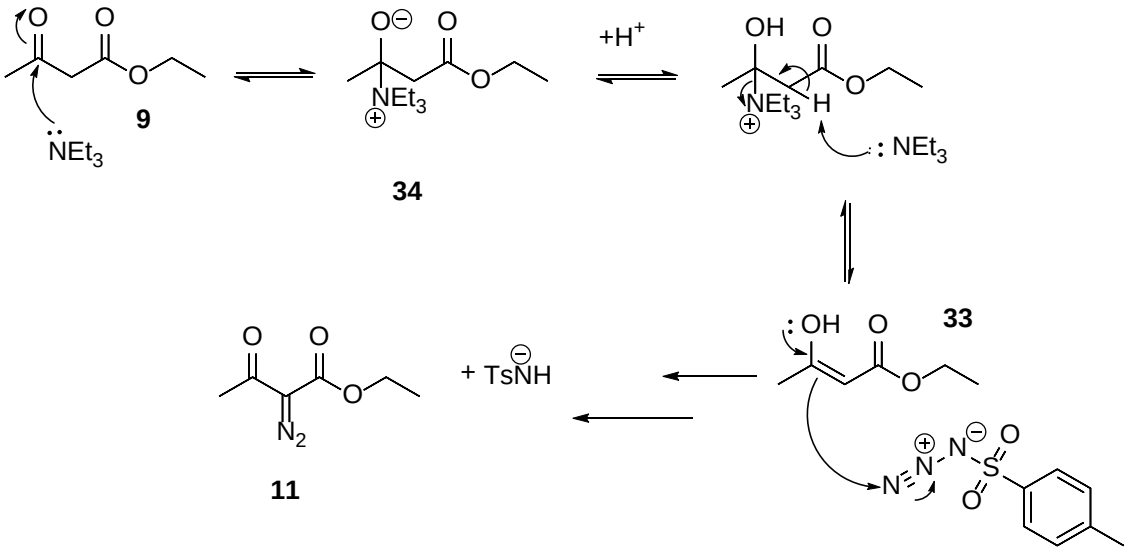
Figure 2.28 Formation of enol tautomer of ethyl acetoacetate **9** promoted in water.

Water-promoted formation of the enol as described above may account for the efficacy of the diazo transfer reaction when catalytic quantities of base are used, as deprotonation can be done by a base molecule or a solvent molecule. Once formed, enols act as nucleophiles to react with *p*-toluenesulfonyl azide **1**, as shown in **Scheme 2.27**.



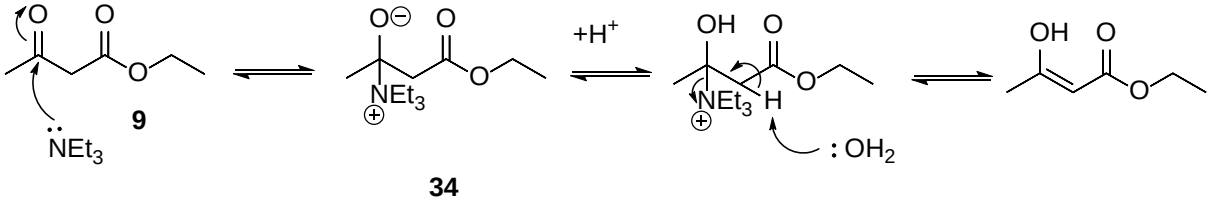
Scheme 2.27

A possible explanation for the efficacy of the reaction in the presence of substoichiometric quantities of base was proposed by Bruice and co-workers in their exploration into an alternative mechanism for enolisation of β-ketoesters.[38] The authors suggested an alternative mechanism for keto-enol tautomerism, where in cases where a tertiary amine base is employed the reaction proceeds *via* a zwitterionic carbinolamine intermediate **34**, which is trapped by protonation. A second molecule of tertiary amine base then catalyses the elimination of both the neutral amine and a proton, resulting in the formation of an enol **33** which can then act as a nucleophile, as illustrated in **Scheme 2.28**.



Scheme 2.28

We propose that this could be further promoted when water is used as reaction solvent, as shown in **Scheme 2.29**, by water facilitating formation of the enol **33** *via* the zwitterionic carbinolamine intermediate **34** thereby recycling the base allowing use of substoichiometric quantities.



Scheme 2.29

Zeta potential is a term to describe the electrochemical potential in colloidal suspensions.[39] Zeta potential is the potential difference between the stationary layer of fluid attached to the dispersed particle and the dispersion medium. The size of the zeta potential between phases in a suspension is dependent on the degree of electrostatic repulsion between adjacent, similarly charged particles in a dispersion.[40] When the potential is small, attractive forces may exceed this repulsion and the dispersion may break and flocculate. When applied to this

project, this may mean that the water solvent molecules in the dispersion of the reaction mixture may agglomerate, forming an effective bubble of organic solvent in which the reaction occurs. This would mean that water is acting as a support, rather than a solvent for the reaction; the reaction takes place on the surface of the solution. This flocculation effect of the water molecules would result in a higher degree of interactions between the reagents, leading to more efficient reactions compared to those carried out in organic solvents where the zeta effect results in a more uniform dispersion. The zeta effect of solutions has also been shown to be effected by the pH of the solution.[41] Therefore, the concentration of base in the solution may also effect the zeta potential of the reaction mixture resulting in a change in the degree of dispersion of the colloidal suspension.

2.7 Conclusions

Diazo transfer has been achieved to a range of β-ketoesters using just a catalytic amount of base in water thus moving towards a green, environmentally friendly method for this transformation, with no significant loss in reactivity. Diazo transfer has also been successfully carried out using a safer polymer bound azide, in water with a catalytic amount of base. This is an improvement over the traditional methods of diazo transfer to these systems which routinely use tosyl azide, 1-2 equivalents of base and organic solvents such as dichloromethane or acetonitrile.

The attractiveness of this method also lies in the use of a safer diazo transfer reagent, non-flammable solvent and simplified workup by filtration of resin bound sulfonamide by-product. All these features make this methodology potentially attractive for use in industry routes in the future.

2.8 References

[1] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev. (Washington, DC, United States)* **2015**, *115*, 9981–10080.

[2] G. Maas, *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 8186–95.

[3] G. Regitz, M.; Maas, *Diazo Compounds: Properties and Synthesis, Academic Press, Orlando*, **1986**.

[4] M. Regitz, *Synthesis (Stuttg).* **1972**, 351–373.

[5] M. Regitz, *Angew. Chemie, Int. Ed. English* **1967**, *6*, 733–749.

[6] F. W. Bollinger, L. D. Tuma, *Synlett* **1996**, 407–413.

[7] L. D. Tuma, *Thermochim. Acta* **1994**, *243*, 161–167.

[8] G. M. Green, N. P. Peet, W. A. Metz, *J. Org. Chem.* **2001**, *66*, 2509–2511.

[9] A. M. Harned, W. M. Sherrill, D. L. Flynn, P. R. Hanson, *Tetrahedron* **2005**, *61*, 12093–12099.

[10] E. D. Goddard-Borger, R. V Stick, *Org. Lett.* **2007**, *9*, 3797–3800.

[11] A. R. Katritzky, M. El Khatib, O. Bol'shakov, L. Khelashvili, P. J. Steel, "Benzotriazol-1-yl-sulfonyl azide for diazotransfer and preparation of azidoacylbenzotriazoles," **2010**.

[12] M. K. Muthyala, S. Choudhary, A. Kumar, *J. Org. Chem.* **2012**, *77*, 8787–8791.

[13] J. C. Anastas, P. T.; Warner, in *Green Chem. Theory Pract.*, Oxford University Press, **1998**.

[14] E. Tarrant, New Insights into the Synthesis of α-Diazocarbonyl Compounds and Their Decomposition Pathways, University College Cork, **2012**.

[15] A. G. Barrett, D. C. Braddock, *Chem. Commun.* **1997**, 351–352.

[16] C.-T. Chen, Y. S. Munot, *J. Org. Chem.* **2005**, *70*, 8625–8627.

[17] R. H. Tale, A. D. Sagar, H. D. Santan, R. N. Adude, *Synlett* **2006**, 415–418.

[18] G. C. M. Kondaiah, L. A. Reddy, K. S. Babu, V. M. Gurav, K. G. Huge, R. Bandichhor, P. P. Reddy, A. Bhattacharya, R. V. Anand, *Tetrahedron Lett.* **2008**, *49*, 106–109.

[19] M. Regitz, in *Newer Methods Prep. Org. Chem.*, **1971**, pp. 81–126.

[20] M. Regitz, G. Maas, *Diazo Compounds. Properties and Synthesis.*, Academic, **1986**.

[21] G. G. Hazen, L. M. Weinstock, R. Connell, F. W. Bollinger, *Synth. Commun.* **1981**, *11*, 947–956.

[22] T. J. Curphey, *Org. Prep. Proced. Int.* **1981**, *13*, 112–115.

[23] A. Regitz, M.; Hocker, J.; Ledhegener, in *A. Org. Synth. Coll. Vol. 5*, John Wiley & Sons: New York, **1973**, pp. 179–183.

[24] D. B. Ramachary, V. V Narayana, K. Ramakumar, *Tetrahedron Lett.* **2008**, *49*, 2704–2709.

[25] M. Kitamura, N. Tashiro, S. Miyagawa, T. Okauchi, *Synthesis (Stuttg).* **2011**, 1037–1044.

[26] M. Presset, D. Mailhol, Y. Coquerel, J. Rodriguez, *Synthesis (Stuttg).* **2011**, 2549–2552.

[27] P. A. Steiner, W. Gordy, *J. Mol. Spectrosc.* **1966**, *21*, 291–301.

[28] A. K. S. Labban, Y. Marcus, *J. Solution Chem.* **n.d.**, *20*, 221–232.

[29] A. Hassner, M. Stern, *Angew. Chemie Int. Ed. English* **1986**, *25*, 478–479.

[30] B. E. Blass, K. R. Coburn, A. L. Faulkner, W. L. Seibel, A. Srivastava, *Tetrahedron Lett.* **2003**, *44*, 2153–2155.

[31] V. Gupta, S. Kabiraj, M. Rane, S. V Bhat, *RSC Adv.* **2015**, *5*, 22951–22956.

[32] Z. Wang, Z. Wang, Y. Bai, B. Fu, H. Liu, A. Song, Z. Zhang, M. Zhang, *Catal. Commun.* **2012**, *27*, 164–168.

[33] S. Li, W. Guo, S. Li, Y. Shang, *Huaxue Shiji* **2010**, *32*, 155–158.

[34] Z. S. Qureshi, K. M. Deshmukh, P. J. Tambade, K. P. Dhake, B. M. Bhanage, *European J. Org. Chem.* **2010**, 6233–6238.

[35] S. M. Nicolle, C. J. Hayes, C. J. Moody, *Chem. - A Eur. J.* **2015**, *21*, 4576–4579.

[36] D. W. Emerson, D. T. Shea, E. M. Sorensen, *Ind. Eng. Chem. Prod. Res. Dev.* **1978**, *17*, 269–274.

[37] J. W. Bunting, J. P. Kanter, *J. Am. Chem. Soc.* **1993**, *115*, 11705–11715.

[38] P. Y. Bruice, *J. Am. Chem. Soc.* **1983**, *105*, 4982–4996.

[39] A. D. Mc Naught, A. Wilkinson, *Iupac* **2012**, 1670.

[40] R. J. Hunter, R. H. Ottewill, R. L. Rowell, *Zeta Potential in the Colloid Science: Principles and Applications*, Elsevier Science, **2013**.

[41] D. Hanaor, M. Michelazzi, C. Leonelli, C. C. Sorrell, *J. Eur. Ceram. Soc.* **2012**, *32*, 235–244.

Chapter 2

Experimental

Table of Contents

2.1 General procedures

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide,[1] ethyl acetate was distilled from potassium carbonate,[2,3] hexane was stored and distilled prior to use.[2] Organic phases were dried using anhydrous magnesium sulphate. All commercial reagents were used without further purification unless otherwise stated.

Proton (400 MHz) and carbon (100 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Proton (600 MHz) and carbon (150 MHz) spectra were recorded on a Bruker Avance III 600 MHz NMR spectrometer using a 5mm Dual C-H cryoprobe. HSQC and HMBC NMR spectra were recorded on Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 ºC) in deuterated chloroform ($CDCl_3$), unless otherwise stated, using tetramethylsilane (TMS) as internal chemical shift reference standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants (*J*) are expressed in Hertz (Hz). Splitting patterns in ^1H spectra are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublets of doublets), dt (doublet of triplets), dq (doublet of quartets) and m (multiplet). ^{13}C NMR spectra were assigned with the aid of DEPT experiments. Compounds which were assigned with the aid of DEPT experiments were assigned by identifying the carbon type (CH_3, CH_2, CH or C).

Infrared spectra were measured as thin films on sodium chloride plates for oils or KBr disks for solids on a Perkin Elmer Spectrum One spectrometer and using universal ATR sampling accessories on a Perkin Elmer Spectrum Two spectrometer, unless otherwise stated. Flash chromatography was performed using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF_{254}). Visualisation was achieved by UV (254 nm) light detection and vanillin staining.

Elemental analyses were performed by the Microanalysis Laboratory, National University Ireland, Cork using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Nominal mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in

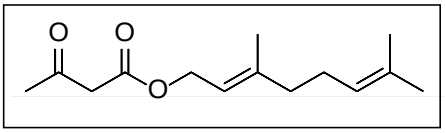
electrospray ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile.

Microwave assisted synthesis was achieved using the CEM Discover Labmate Synthesiser in conjunction with Synergy software. Flow chemistry experiments were performed on a Vapourtec R-Series, equipped with two acid-resistant pumps, two injector units and PFA tubular reactor coils.

2.2 Synthesis of α-diazocarbonyl compounds

2.2.1 Preparation of ester derivatives

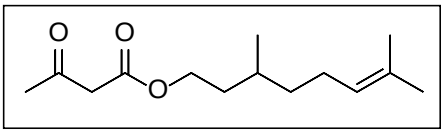
Note: Non-commercial esters were prepared by transesterification with 3-nitrobenzeneboranic acid.[1] Despite repeated column chromatography, ~10% of the enol tautomer is present in the sample. Characteristic signals for the enol form are present at 5ppm in the ^{1}H NMR spectrum and at 22, 63, 90, 173 and 176 ppm in the ^{13}C NMR spectrum for these samples.



(*E*)-3,7-Dimethylocta-2,6-dien-1-yl 3-oxobutanoate[2] 3

Geraniol **35** (1.50 g, 9.75 mmol) was added to a stirring solution of ethyl acetoacetate **9** (1.27 g, 9.75 mmol) in toluene (50 mL). 3-Nitrobenzeneboranic acid **8** (41 mg, 244 µmol, 2.5 mol %) was then added as catalyst. The reaction was heated under reflux (150 °C) with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. TLC analysis after 5 h indicated complete consumption of the ethyl acetoacetate **9** and, after cooling, the toluene was removed under reduced pressure to give a yellow oil. Following column chromatography on silica gel using 90:10 hexane: ethyl acetate the product, 3,7-dimethyloct-6-enyl 3-oxobutanoate **3,** was obtained as a yellow oil (1.92g, 83%). δ_H($CDCl_3$, 400 MHz): 1.60 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.02-2.12 (4H, m, 2 x C*H*$_2$), 2.27 [3H, s, C(O)C*H*$_3$], 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.66 (2H, d, OC*H*$_2$, *J* 7.3), 5.08 [1H, m, C*H*=C(CH$_3$)$_2$], 5.35 [1H, m, OCH$_2$C*H*=C(CH$_3$)]; δ_C($CDCl_3$, 100 MHz): 16.5 (*C*H$_3$), 17.7 (*C*H$_3$), 25.7 (*C*H$_3$), 26.2 (*C*H$_2$), 28.3 (*C*H$_3$), 39.5 (*C*H$_2$), 50.1 [C(O)*C*H$_2$C(O)], 62.2 (O*C*H$_2$), 117.6 (*C*H) alkene, 123.6 (*C*H) alkene, 131.9 (*C*$_q$), 143.5 (*C*$_q$), 167.1 (*C*=O) ester, 200.6 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1738, 1716, 1646; *m/z* (ES+) 261.3 [($C_{14}H_{22}O_3$+Na)$^+$, 100%], (ES-) 237.4 [($C_{14}H_{22}O_3$-H)$^-$, 35%].

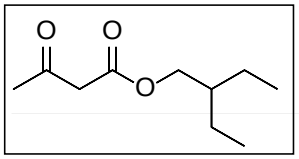
Spectral characteristics were consistent with those previously reported.[2]



3,7-Dimethyloct-6-en-1-yl 3-oxobutanoate[2] **4**

The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **3** using citronellol **36** (2.67 g, 17.05 mmol), ethyl acetoacetate **9** (2.22 g, 17.05 mmol) and 3-nitrobenzeneboranic acid **8** (71 mg, 426 µmol, 2.5 mol %) in toluene (60 mL). The reaction was heated under reflux for 5 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-stark distillation apparatus. The reaction mixture was allowed to cool to room temperature. The toluene was removed *in vacuo*. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (80:20) as eluent, 3,7-dimethyloct-6-en-1-yl 3-oxobutanoate **4** was isolated as a pale yellow oil (3.28 g, 80 %). δ_H($CDCl_3$, 400 MHz): 0.91 (3H, d, CHC*H*$_3$, *J* 6.7), 1.14-1.80 [11H, m, containing 1.60 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$)], 1.90-2.02 (2H, m, OCH_2CH_2), 2.27 [3H, s, C(O)C*H*$_3$], 3.44 [2H, s, C(O)C*H*$_2$C(O)], 4.13-4.23 (2H, m, OC*H*$_2$), 5.08 [1H, t, C*H*=C$(CH_3)_2$, *J* 7.2]; δ_C($CDCl_3$, 100 MHz): 17.6 (*C*H_3), 19.3 (*C*H_3), 25.3 (*C*H_2), 25.7 (*C*H_3), 29.4 (*C*H_3), 30.0 (*C*H), 35.3 (*C*H_2), 36.9 (*C*H_2), 50.1 [C(O)*C*H_2C(O)], 63.9 (O*C*H_2), 124.6 (*C*H) alkene, 131.3 (C_q) alkene, 167.2 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1740, 1716, 1649; *m/z* (ES+) 263.3 [$(C_{14}H_{24}O_3+Na)^+$, 100%], 304.3 [$(C_{14}H_{24}O_3+MeCN+Na)^+$, 15%], (ES-) 239.4 [$(C_{14}H_{24}O_3-H)^-$, 25%],

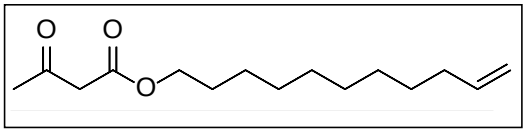
Spectral characteristics were consistent with those previously reported.[2]



2-Ethylbutyl 3-oxobutanoate[4] **5**

The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **3** using 2-ethylbutan-1-ol **38** (2.01 g, 19.63 mmol), ethyl acetoacetate **9** (2.55 g, 19.63 mmol) and 3-nitrobenzeneboranic acid **8** (82 mg, 491 µmol, 2.5 mol %) in toluene (50 mL). The reaction was heated under reflux for 5 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-stark distillation apparatus. The toluene was removed under reduced pressure. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (80:20) as eluent, 2-ethylbutyl 3-oxobutanoate **5** was isolated as a dark yellow oil (2.97 g, 82 %). δ_H($CDCl_3$, 400 MHz): 0.90 (6H, t, 2 x C*H*$_3$, *J* 7.5), 1.32-1.55

(4H, m, 2 x C*H*$_2$CH$_3$), 1.49-1.58 (1H, m, C*H*), 2.28 [3H, s, C(O)C*H*$_3$], 3.46 [2H, s, C(O)C*H*$_2$C(O)], 4.07 (2H, d, OC*H*$_2$, *J* 5.8); δ_C(CDCl$_3$, 100 MHz): 10.9 (2 x *C*H$_3$), 23.1 (2 x *C*H$_2$), 30.9 (*C*H$_3$), 40.3 (*C*H), 50.1 [C(O)*C*H$_2$C(O)], 67.4 (O*C*H$_2$), 167.3 (*C*=O) ester, 200.6 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1739, 1716, 1649; *m/z* (ES+) 209.3 [(C$_{10}$H$_{18}$O$_3$+Na)$^+$, 37%], 250.3 [(C$_{10}$H$_{18}$O$_3$+MeCN+Na)$^+$, 100%], (ES-) 185.4 [(C$_{10}$H$_{18}$O$_3$-H)$^-$, 15%].



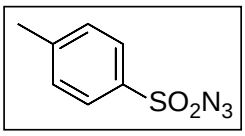
Undec-10-en-1-yl 3-oxobutanoate[3] **6**

The title compound was prepared following the procedure described for 3,7-dimethyloct-6-enyl 3-oxobutanoate **3** using undec-10-en-ol **37** (2.49 g, 14.66 mmol), ethyl acetoacetate **9** (1.91 g, 14.66 mmol) and 3-nitrobenzeneboranic acid **8** (61 mg, 367 µmol, 2.5 mol %) in toluene (60 mL). The reaction was heated under reflux for 18 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-stark distillation apparatus. The reaction mixture was allowed to cool to room temperature. The toluene was removed *in vacuo*. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (80:20) as eluent, undec-10-en-1-yl 3-oxobutanoate **6** was isolated as a pale yellow oil (3.12 g, 84 %). δ_H(CDCl$_3$, 400 MHz): 1.24-1.39 (12H, m, 6 x C*H*$_2$), 1.61-1.68 (2H, m, C*H*$_2$), 2.01-2.06 (2H, m, C*H*$_2$), 2.27 [3H, s, C(O)C*H*$_3$], 3.44 [2H, s, C(O)C*H*$_2$C(O)], 4.13 (2H, t, OC*H*$_2$, *J* 6.8), 4.91-5.02 (2H, m, CH=C*H*$_2$), 5.76-5.86 (1H, m, C*H*=CH$_2$); δ_C(CDCl$_3$, 75.5 MHz): 25.7 (*C*H$_2$), 28.5 (*C*H$_2$), 28.9 (*C*H$_2$), 29.0 (*C*H$_2$), 29.1 (*C*H$_2$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 30.1 (*C*H$_3$), 33.8 (*C*H$_2$), 50.1 [C(O)*C*H$_2$C(O)], 65.5 (O*C*H$_2$), 114.1 (*C*H$_2$) alkene, 139.1 (*C*H) alkene, 167.2 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1741, 1718, 1640; *m/z* (ES+) 277.3 [(C$_{15}$H$_{26}$O$_3$+Na)$^+$, 100%], (ES-) 253.4 [(C$_{15}$H$_{26}$O$_3$-H)$^-$, 95%].

Spectral characteristics were consistent with those previously reported.[3]

2.2.2 Synthesis of tosyl azide

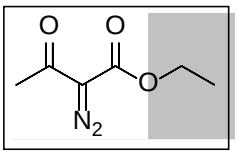
Caution: Diazo transfer reagents are potentially hazardous reagents and extreme care should be taken in their use.[5–7] They are shock sensitive and in the case of tosyl azide, which is a solid below room temperature, it should not be scraped out of its container as it may explode. Tosyl azide should be stored in the freezer, and when using, it is best to allow it to warm to melting point (*ca.* 20 °C) and then pipette it out of its container using a clean pasteur pipette which has no sharp edges. The preparation or concentration of solutions containing diazo transfer reagents was carried out in a well ventilated fumehood behind a safety shield. For safety reasons only one batch of tosyl azide was made and stored in the lab at any one time.



_p_-Toluenesulfonyl azide[8] **1**

A solution of *p*-toluenesulfonyl chloride **10** (12.23 g, 65.0 mmol) in acetone (30 mL) was added dropwise over 15 min to a stirring solution of sodium azide (4.34 g, 66.0 mmol) in water (15 mL). The reaction mixture was stirred at room temperature for 2 h after which time the acetone was removed under reduced pressure. The aqueous solution was extracted with dichloromethane (20 mL) and the organic layer was then washed with water (2 x 20 mL) and brine (10 mL). The organic layer was dried and concentrated under reduced pressure to give pure *p*-toluenesulfonyl azide **1** as a colourless oil (11.97 g, 98 %) which crystallised to a white solid on refrigeration; δ_H($CDCl_3$, 400 MHz) 2.48 (3H, s, C*H*$_3$), 7.38-7.86 (4H, m, Ar*H*); ν_{max}(film)/cm^{-1} 2127, 1370, 1167.

2.2.3 Diazo transfer reactions to β-ketoesters

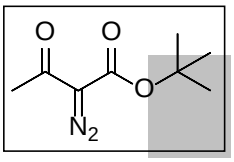


Ethyl 2-diazo-3-oxobutanoate[9] **11**

Triethylamine (0.55 mL, 3.97mmol) was added to a stirring solution of ethyl 3-oxobutanoate **9** (0.52 g, 3.97 mmol) in acetonitrile (20 mL). After 2 min a solution of *p*-toluenesulfonyl azide **1** (0.78 g, 3.97 mmol) in acetonitrile (5 mL) was added dropwise, at room temperature, over 15 min to give a pale yellow solution. The reaction was stirred overnight under an inert nitrogen atmosphere. After 18 h TLC analysis showed complete consumption of the ester starting material **9** and the reaction mixture was

concentrated under reduced pressure. The resulting cream residue was dissolved in ether (30 mL) and washed with 9 % KOH (3 x 30 mL) followed by brine (1 x 30 mL) and water (1 x 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to ethyl 2-diazo-3-oxobutanoate **11** as a yellow oil (0.56 g, 90 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 1.34 (3H, t, OCH_2CH_3, *J* 7.1), 2.48 [3H, s, $C(O)CH_3$], 4.31 (2H, q, OCH_2CH_3, *J* 7.1); δ_C($CDCl_3$, 100 MHz): 14.3 (CH_3), 28.2 (CH_3), 61.4 (OCH_2), 76.4 ($C=N_2$), 161.4 (*C*=O) ester, 190.2 (*C*=O) ketone; ν_{max}(film)/cm^{-1} 2138, 1720, 1660; *m/z* (ES-) 155.2 [$C_6H_8N_2O_3$-H)$^-$, 10%].

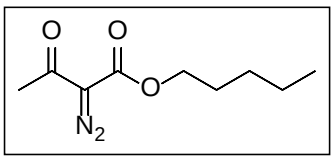
Spectral characteristics were consistent with those previously reported.[9]



t-Butyl 2-diazo-3-oxobutanoate[10] 12

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (1.77 mL, 12.66 mmol), *tert*-butyl 3-oxobutanoate **23** (2.00 g, 12.66 mmol) in acetonitrile (30 mL), and *p*-toluenesulfonyl azide **1** (2.50 g, 12.66 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 16 h TLC analysis showed complete consumption of the ester starting material **23.** Following the work-up tert-butyl 2-diazo-3-oxobutanoate **12** was obtained as a yellow oil (2.15 g, 92 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 1.53 (9H, s, 3 x CH_3 of *t*-butyl), 2.45 [3H, s, $C(O)CH_3$]; δ_C($CDCl_3$, 100 MHz): 28.1 (CH_3), 28.2 (CH_3 x 3 of *t*-butyl), 83.1 (C_q), 160.6 (*C*=O) ester, 190.5 (*C*=O) ketone; no signal observed for ($C=N_2$); ν_{max}(film)/cm^{-1} 2137, 1719, 1658; *m/z* (ES+) 248.2 [($C_8H_{12}O_3N_2$+MeCN+Na)$^+$, 70%], (ES-) 183.3 [($C_8H_{12}O_3N_2$-H)$^-$, 25%].

Spectral characteristics were consistent with those previously reported.[10]

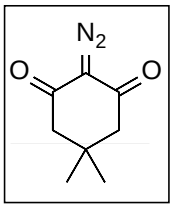


Pentyl 2-diazo-3-oxobutanoate[11] 13

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (0.41 mL, 2.93 mmol), pentyl 3-oxobutanoate **28** (0.51 g, 2.93 mmol) in acetonitrile (15 mL), and *p*-toluenesulfonyl azide **1** (0.58 g, 2.93 mmol) dissolved in

acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 16 h TLC analysis showed complete consumption of the ester starting material **28.** Following the work-up pentyl 2-diazo-3-oxobutanoate **13** was obtained as a yellow oil (0.52 g, 90 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.92 (3H, t, CH_2CH_3 *J* 6.6), 1.32-1.39 (4H, m, 2 x CH_2), 1.65-1.74 (2H, m, CH_2), 2.52 [3H, s, C(O)CH_3], 4.24 (2H, t, OCH_2CH_2, *J* 6.7); δ_C($CDCl_3$, 100 MHz): 13.9 (CH_3), 22.2 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 28.3 (CH_3), 65.6 (OCH_2), 161.5 (*C*=O) ester, 190.2 (*C*=O) ketone; no signal observed for (*C*=N_2); ν_{max}(film)/cm^{-1} 2140, 1719, 1660; *m/z* (ES+) 262.3 [($C_9H_{14}O_3N_2$+MeCN+Na)$^+$, 100%], (ES-) 197.3 [($C_9H_{14}O_3N_2$-H)$^-$, 20%].

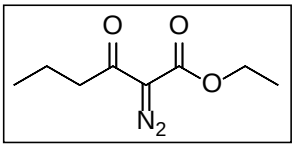
Spectral characteristics were consistent with those previously reported.[11]



2-Diazo-5,5-dimethylcyclohexane-1,3-dione[14] **14**

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (0.50 mL, 3.58 mmol), dimedone **20** (0.50 g, 3.58 mmol) in acetonitrile (15 mL), and *p*-toluenesulfonyl azide **1** (0.71 g, 3.58 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 18 h TLC analysis showed complete consumption of the ketone starting material **20.** In this case, following removal of acetonitrile *in vacuo*, the residue was dissolved in DCM, and the work up was carried out as above. Following the work-up 2-diazo-5,5-dimethylcyclohexane-1,3-dione **14** was obtained as a white solid (0.51 g, 85 %), which was used without further purification. δ_H($CDCl_3$, 300 MHz): 1.13 (6H, s, 2 x CH_3), 2.45 (4H, s, 2 x CH_2); δ_C($CDCl_3$, 75.5 MHz): 28.3 (2 x CH_2), 31.1 (C_q), 50.5 (2 x CH_3), 83.6 (*C*=N_2), 189.79 (*C*=O); ν_{max}(KBr)/cm^{-1} 2143, 1639; *m/z* (ES+) 189.3 [($C_8H_{10}O_2N_2$+Na)$^+$, 20%]. Found C 57.77, H 6.07, N, 16.88%; $C_8H_{10}O_2N_2$ requires C 57.82, H 6.07, N 16.86%; mp 105-107 °C, Lit[15] mp 106-108 °C.

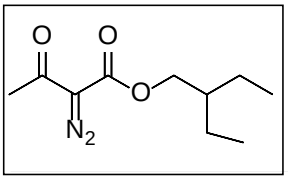
Spectral characteristics were consistent with those previously reported.[14]



Ethyl 2-diazo-3-oxohexanoate[12] **15**

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (0.45 mL, 3.19 mmol), ethyl 3-oxohexanoate **29** (0.51 g, 3.19 mmol) in acetonitrile (10 mL), and *p*-toluenesulfonyl azide **1** (0.63 g, 3.19 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 16 h TLC analysis showed complete consumption of the ester starting material **29.** Following the work-up ethyl 2-diazo-3-oxohexanoate **15** was obtained as a yellow oil (0.47 g, 80 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.96 (3H, t, C*H*$_3$, *J* 7.5), 1.34 (3H, t, OCH$_2$C*H*$_3$, *J* 7.2), 1.62-1.71 [2H, m, C(O)CH$_2$C*H*$_2$], 2.83 [2H, t, C(O)C*H*$_2$CH$_2$, *J* 7.2], 4.31 (2H, q, OC*H*$_2$CH$_3$, *J* 7.2); δ_C($CDCl_3$, 100 MHz): 13.7 (*C*H$_3$), 14.3 (*C*H$_3$), 17.8 (*C*H$_2$), 42.0 [C(O)*C*H$_2$], 51.3 (O*C*H$_2$), 75.8 (*C*=N$_2$), 161.4 (*C*=O) ester, 192.8 (*C*=O) ketone; ν_{max}(film)/cm^{-1} 2137, 1719, 1658; *m/z* (ES+) 185.3 [($C_8H_{12}O_3N_2$+H)$^+$, 15%], 207.3 [($C_8H_{12}O_3N_2$+MeCN+Na)$^+$, 100%], (ES-) 183.3 [($C_8H_{12}O_3N_2$-H)$^-$, 25%].

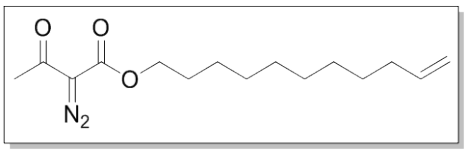
Spectral characteristics were consistent with those previously reported.[12]



2-Ethylbutyl 2-diazo-3-oxobutanoate[11] **16**

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (0.38 mL, 2.71 mmol), 2-ethylbutyl 3-oxobutanoate **5** (0.51 g, 2.71 mmol) in acetonitrile (15 mL), and *p*-toluenesulfonyl azide **1** (0.54 g, 2.71 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 16 h TLC analysis showed complete consumption of the ester starting material **5.** Following the work-up 2-ethylbutyl 2-diazo-3-oxobutanoate **16** was obtained as a yellow oil (0.44 g, 76%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.92 (6H, t, 2 x C*H*$_3$, *J* 7.4), 1.32-1.48 (4H, m, 2 x C*H*$_2$), 1.53-1.61 (1H, m, C*H*), 2.48 [3H, s, C(O)C*H*$_3$], 4.18 (2H, d, OC*H*$_2$, *J* 5.7); δ_C($CDCl_3$, 100 MHz): 11.0 (2 x *C*H$_3$), 23.2 (2 x *C*H$_2$), 28.3 (*C*H$_3$), 40.4 (*C*H), 67.4 (O*C*H$_2$), 161.6 (*C*=O) ester, 190.1 (*C*=O) ketone; no signal observed for (*C*=N$_2$); ν_{max}(film)/cm^{-1} 2139, 1719, 1660; *m/z* (ES+) 213.4 [($C_{10}H_{16}O_3N_2$+H)$^+$, 10%], 235.3 [($C_{10}H_{16}O_3N_2$+Na)$^+$, 100%], (ES-) 211.3 [($C_{10}H_{16}O_3N_2$-H)$^-$, 20%].

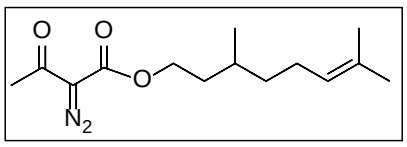
Spectral characteristics were consistent with those previously reported.[11]



Undec-10-en-1-yl 2-diazo-3-oxobutanoate[11] 17

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (0.28 mL, 1.97 mmol), undec-10-en-1-yl 3-oxobutanoate **6** (0.50 g, 1.97 mmol) in acetonitrile (15 mL), and *p*-toluenesulfonyl azide **1** (0.39 g, 1.97 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 16 h TLC analysis showed complete consumption of the ester starting material **6.** Following the work-up undec-10-en-1-yl 2-diazo-3-oxobutanoate **17** was obtained as a yellow oil (0.49 g, 89%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 1.29-1.48 (12H, m, 6 x C*H*$_2$), 1.65-1.75 (2H, m, C*H*$_2$), 2.01-2.06 (2H, m, C*H*$_2$), 2.48 [3H, s, C(O)C*H*$_3$], 4.23 (2H, t, OC*H*$_2$, *J* 6.6), 4.92-5.10 (2H, m, CH=C*H*$_2$), 5.76-5.90 (1H, m, C*H*=CH$_2$); δ_C($CDCl_3$, 75.5 MHz): 25.8 (*C*H$_2$), 28.6 (*C*H$_3$), 28.9 (*C*H$_2$), 29.1 (*C*H$_2$), 29.1 (*C*H$_2$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 29.37 (*C*H$_2$), 33.6 (*C*H$_2$), 65.5 (O*C*H$_2$), 114.1 (*C*H$_2$) alkene, 139.1 (*C*H) alkene, 161.5 (*C*=O) ester, 190.1 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max}(film)/cm^{-1} 2138, 1719, 1660; *m/z* (ES+) 281.3 [($C_{15}H_{24}O_3N_2$+H)$^+$, 15%] 303.3 [($C_{15}H_{24}O_3N_2$+Na)$^+$, 35%].

Spectral characteristics were consistent with those previously reported.[11]

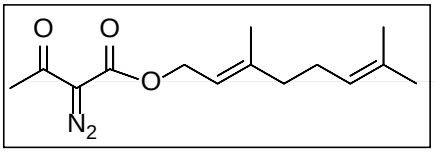


3,7-Dimethyloct-6-enyl 2-diazo-3-oxobutanoate[11] 18

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (0.29 mL, 2.11 mmol), 3,7-dimethyloct-6-enyl 3-oxobutanoate **4** (0.51 g, 2.11 mmol) in acetonitrile (15 mL) and *p*-toluenesulfonyl azide **1** (0.42 g, 2.11 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred at room temperature under an inert nitrogen atmosphere overnight. Following the work-up 3,7-dimethylocta-6-enyl 2-diazo-3-oxobutanoate **18** was obtained as a bright yellow oil (0.51 g, 90 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.93 (3H, d, CHC*H*$_3$, *J* 6.3), 1.16-1.85 [11H, m, containing 1.61 (3H, s, C*H*$_3$), 1.68 (3H, s, C*H*$_3$)], 1.89-2.08 (2H, m, C*H*$_2$), 2.48 [3H, s, C(O)C*H*$_3$], 4.25-4.33 (2H, m, OC*H*$_2$), 5.08 [1H, m, C*H*=C(CH$_3$)$_2$,]; δ_C($CDCl_3$, 100 MHz): 17.7 (*C*H$_3$), 19.4

(*C*H_3), 25.3 (*C*H_2), 25.7 (*C*H_3), 28.3 (*C*H_3), 29.4 (*C*H), 29.9 (*C*H_2), 35.5 (*C*H_2), 36.9 (*C*H_2), 64.0 (O*C*H_2), 124.3 (*C*H) alkene, 131.6 (C_q) alkene, 161.5 (*C*=O) ester, 190.2 (*C*=O) ketone; no signal observed for (*C*=N_2); ν_{max}(film)/cm^{-1} 2139, 1719, 1660; *m/z* (ES+) 289.3 [($C_{14}H_{22}O_3N_2$+Na)$^+$, 80%], 330.3 [($C_{14}H_{22}O_3N_2$+MeCN+Na)$^+$, 15%].

Spectral characteristics were consistent with those previously reported.[11]



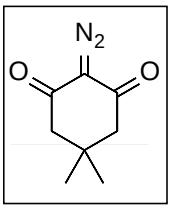
(*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-diazo-3-oxobutanoate[13] **19**

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** using triethylamine (0.29 mL, 2.11 mmol), 3,7-dimethyloct-6-enyl 3-oxobutanoate **3** (0.50 g, 2.11 mmol) in acetonitrile (15 mL), and *p*-toluenesulfonyl azide **1** (0.42 g, 2.11 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 16 h TLC analysis showed complete consumption of the ester starting material **3.** Following the work-up (E)-3,7-dimethylocta-2,6-dien-1-yl 2-diazo-3-oxobutanoate **19** was obtained as a yellow oil (0.51 g, 92 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 1.53 (3H, s, C*H*$_3$), 1.61 (3H, s, C*H*$_3$), 1.66 (3H, s, C*H*$_3$), 1.92-2.12 (4H, m, 2 x C*H*$_2$), 2.41 [3H, s, C(O)C*H*$_3$], 4.68 (2H, d, OC*H*$_2$, *J* 7.1), 5.00 [1H, m, C*H*=C(CH_3)$_2$], 5.29 [1H, m, OCH_2C*H*=C(CH_3)]; δ_C($CDCl_3$, 300 MHz): 16.5 (*C*H_3), 17.7 (*C*H_3), 25.6 (*C*H_3), 26.2 (*C*H_2), 28.2 (*C*H_3), 39.5 (*C*H_2), 62.1 (O*C*H_2), 117.7 (*C*H) alkene, 123.5 (*C*H) alkene, 131.9 (C_q) alkene, 143.4 (C_q) alkene, 161.4 (*C*=O) ester, 190. (*C*=O) ketone; no signal observed for (*C*=N_2); ν_{max}(film)/cm^{-1} 2136, 1713, 1658; *m/z* (ES+) 287.3 [($C_{14}H_{20}O_3N_2$+Na)$^+$, 100%], 328.3 [($C_{14}H_{20}O_3N_2$+MeCN+Na)$^+$, 85%], (ES-) 263.3 ($C_{14}H_{20}O_3N_2$-H)$^-$, 10%].

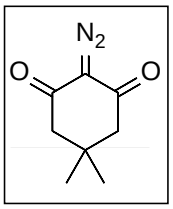
Spectral characteristics were consistent with those previously reported.[13]

2.3 Diazo transfer as a greener process

2.3.1 Comparison of literature results



DMAP (8 mg, 0.06 mmol, 5 mol %) was added to a stirring solution of dimedone **20** (0.18 g, 1.29 mmol) in acetonitrile (4 mL). After 2 min a solution of *p*-toluenesulfonyl azide **1** (0.26 g, 1.29 mmol) in acetonitrile (1 mL) was added dropwise, at room temperature, over 15 min to give a pale yellow solution. The reaction was stirred for 1h under an inert nitrogen atmosphere. The acetonitrile was removed under reduced pressure, giving a cream coloured residue. This was dissolved in 15 mL diethyl ether and washed with 2 x 15 mL water. The organic layer was dried with $MgSO_4$ and filtered, before the ether was removed *in vacuo*. Following column chromatography on silica gel using 65:35 hexane: ethyl acetate, 2-diazo-5,5-dimethylcyclohexane-1,3-dione **14** was obtained as an off-white solid (4.6 mg, 2.5%). Spectral details as listed previously.



DMAP (7 mg, 0.06 mmol, 5 mol %) was added to a stirring solution of dimedone **20** (0.15 g, 1.10 mmol) in dichloromethane (4 mL). After 2 min a solution of *p*-toluenesulfonyl azide **1** (0.22 g, 1.10 mmol) in dichloromethane (1 mL) was added dropwise, at room temperature, over 15 min to give a colourless solution. The reaction was stirred for 2h under an inert nitrogen atmosphere. The reaction mixture was transferred to a separating funnel and washed with 2 x 15 mL water. The organic layer was dried with $MgSO_4$ and filtered, before the ether was removed *in vacuo*. Following column chromatography on silica gel using 70:30 hexane: ethyl acetate, 2-diazo-5,5-dimethylcyclohexane-1,3-dione **14** was obtained as an off-white solid (15.3 mg, 8.4%). Spectral details as listed previously.

Literature results[16]

Substrate	*D.T. Reagent*	*Solvent*	*Base*	*Reaction Time (h)*	*Yield*[1]
Dimedone	TsN_3	CH_3CN	DMAP	1	94%
Dimedone	TsN_3	CH_2Cl_2	DMAP	2	90%

[1] % Yields reported following column chromatography on silica gel

Experimental results

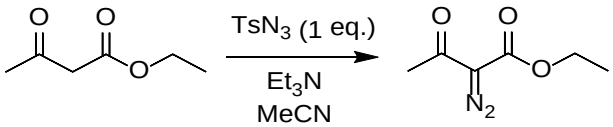
Substrate	*D.T. Reagent*	*Solvent*	*Base*	*Reaction Time (h)*	*Yield*[1]
Dimedone	TsN_3	CH_3CN	DMAP	1	3%
Dimedone	TsN_3	CH_2Cl_2	DMAP	2	8%

[1] % Yields reported following column chromatography on silica gel

2.3.2 Initial investigation into using sub-stoichiometric quantities of base

Representative procedure

A solution of tosyl azide **1** (0.31 g, 1.55 mmol) in 5 mL acetonitrile was added dropwise to a stirring solution of ethyl acetoacetate **9** (0.20 g, 1.55 mmol) and triethylamine (0.22 mL, 1.55 mmol) in 10 mL acetonitrile. The reaction was stirred under an inert nitrogen atmosphere for 5h. At this point, the acetonitrile was removed *in vacuo*. The resulting yellow residue was dissolved in ether (20 mL) and washed with 9 % KOH (3 x 15 mL) followed by water (1 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a bright yellow oil. No starting material was observed in the ^1H NMR spectrum of products, therefore each reaction was repeated as above, but with no KOH work up. ^1H NMR spectrum was obtained after acetonitrile was removed *in vacuo*. Results are outlined below, with spectral details as listed previously.

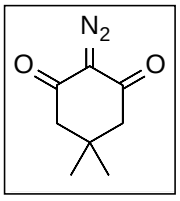


9 **11**

Entry	*Reaction Time*	*Et_3N Loading*	*Concentration*	*Conversion[1]*
1	5h	100 mol%	0.10 mol/ L	93%
2	5h	50 mol%	0.11 mol/ L	86%
3	5h	5 mol%	0.11 mol/ L	24%
4	5h	1 mol%	0.11 mol/ L	8%

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

2.3.3 Investigation into effects of solvent/base choice



2.3.3.1 Dimedone

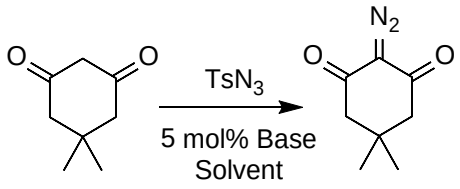
Representative procedure for reactions carried out in organic solvents

A solution of tosyl azide **1** (0.23 g, 1.19 mmol) in 0.5 mL acetonitrile was added to a stirring solution of dimedone **20** (0.17 g, 1.19 mmol) and DMAP (7.3 mg, 60 µmol, 5 mol%) in 4.5 mL acetonitrile. This solution was stirred at room temperature under an inert nitrogen atmosphere for 18h. At this time TLC analysis showed no evidence of starting material. The solvent was then removed *in vacuo* in order to obtain a ^{1}H NMR spectrum. Due to the structure of dimedone, it was difficult to confirm conversion to product by ^{1}H NMR spectroscopy of the crude product. Samples were purified by column chromatography on silica gel, using 80:20 hexane: ethyl acetate to give 2-diazo-5,5-dimethylcyclohexane-1,3-dione as an off-white solid **14**. Spectral details as listed previously.

Representative procedure for reactions carried out in water

A solution of tosyl azide **1** (0.17 g, 0.89 mmol) in 1 mL water was added to a stirring solution of dimedone **20** (0.11 g, 0.70 mmol) and triethylamine (6.2 µL, 44.3 µmol, 5 mol%) in 4 mL

water. This solution was stirred at room temperature under an inert nitrogen atmosphere for 18.5h. At this time TLC analysis showed no evidence of starting material. The reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried and filtered. The solvent was then removed *in vacuo*. Due to the structure of dimedone, it was difficult to confirm conversion to product by ^{1}H NMR of the crude product. Samples were purified by column chromatography on silica gel, using 80:20 hexane: ethyl acetate to give 2-diazo-5,5-dimethylcyclohexane-1,3-dione as an off-white solid **14**. Spectral details as listed previously.



20 **14**

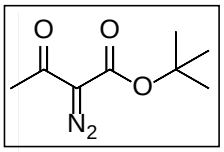
Entry	***Solvent***	***Volume***	***Time***	***Base***	***Yield[1]***
1	Acetonitrile	5 mL	18h	DMAP	98%[2]
2	Acetonitrile	5 mL	18h	Et_3N	96%[2]
3	Dichloromethane	5 mL	18.5h	DMAP	75%
4	Dichloromethane	5 mL	18h	Et_3N	64%
5	Water	5 mL	18h	DMAP	48%
6	Water	5 mL	18.5h	Et_3N	51%
7	Ethanol	5 mL	18h	DMAP	72%
8	Ethanol	5 mL	18h	Et_3N	68%
9	Acetonitrile	5 mL	18h	K_2CO_3	57%
10	Water	5 mL	18h	K_2CO_3	78%
11	Water	1.5 mL	18h	K_2CO_3	6%

[1] % Yields reported following column chromatography on silica gel

[2] These samples contain ~5% *p*-toluenesulfonyl amide.

2.3.3.2 t-Butyl acetoacetate

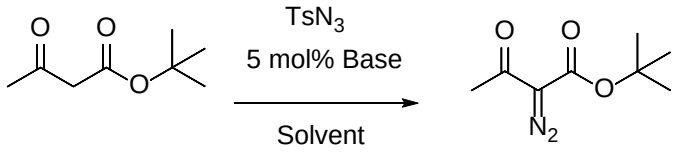
Representative procedure for reactions carried out in organic solvents



A solution of tosyl azide **1** (0.13 g, 0.67 mmol) in 1 mL acetonitrile was added to a stirring solution of *t*-butyl acetoacetate **23** (0.11 g, 0.67 mmol) and DMAP (4.1 mg, 34 µmol, 5 mol %) in 4 mL acetonitrile. This solution was stirred at room temperature under an inert nitrogen atmosphere for 20h. At this time TLC analysis showed no evidence of starting material. The solvent was then removed *in vacuo* in order to obtain a ^{1}H NMR spectrum. Spectral details as listed previously.

Representative procedure for reactions carried out in water

A solution of tosyl azide **1** (0.14 g, 0.70 mmol) in 1 mL water was added to a stirring solution of *t*-butyl acetoacetate **23** (0.11 g, 0.70 mmol) and DMAP (3.6 mg, 35.7 µmol, 5 mol %) in 4 mL water. This solution was stirred at room temperature under an inert nitrogen atmosphere for 19h. At this time TLC analysis showed no evidence of starting material. The reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried and filtered. The solvent was then removed *in vacuo*. Spectral details as listed previously.



23 **12**

Entry	*Solvent*	*Volume*	*Time*	*Base*	*Conversion*[1]
1	Acetonitrile	5 mL	20h	DMAP	99%
2	Acetonitrile	5 mL	20h	Et_3N	93%
3	Dichloromethane	5 mL	20.5h	DMAP	98%
4	Dichloromethane	5 mL	20.5h	Et_3N	97%[2]
5	Water	5 mL	20h	DMAP	74%
6	Water	1.5 mL	20h	DMAP	95%
7	Water	5 mL	20h	Et_3N	60%
8	Water	1.5 mL	20h	Et_3N	100%
9	Ethanol	5 mL	21h	DMAP	100%
10	Ethanol	5 mL	21h	Et_3N	–[3]
11	Acetonitrile	5 mL	20h	K_2CO_3	90%
12	Water	5 mL	20h	K_2CO_3	14%
13	Water	1.5 mL	20h	K_2CO_3	9%

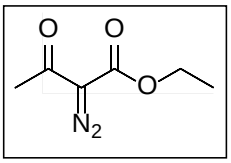
[1] Conversions calculated from ratio of starting material to product using 9H singlet of *t*-butyl group in the ^1H NMR spectrum of the crude reaction mixture.

[2] Singlets observed at 1.6 ppm and 2.7 ppm which do not correspond to any reagents or expected by-products of the reaction.

[3] No starting material remains, however unknown compound in crude reaction mixture with peaks at 1.38 ppm (t), 1.58 ppm (s) 2.79 ppm (s) and 3.17 ppm (q).

2.3.3.3 Ethyl acetoacetate

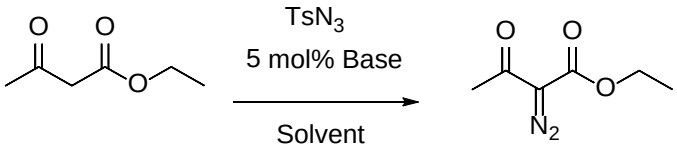
Representative procedure for reactions carried out in organic solvents



A solution of tosyl azide **1** (0.16 g, 0.83 mmol) in 1 mL acetonitrile was added to a stirring solution of ethyl acetoacetate **9** (0.11 g, 0.83 mmol) and DMAP (5.1 mg, 42 µmol, 5 mol %) in 4 mL acetonitrile. This solution was stirred at room temperature under an inert nitrogen atmosphere for 20h. At this time TLC analysis showed no evidence of starting material. The solvent was then removed *in vacuo* in order to obtain a ^{1}H NMR spectrum. Spectral details as listed previously.

Representative procedure for reactions carried out in water

A solution of tosyl azide **1** (0.15 g, 0.78 mmol) in 1 mL water was added to a stirring solution of ethyl acetoacetate **9** (0.10 g, 0.78 mmol) and DMAP (4.7 mg, 38.9 µmol, 5 mol %) in 4 mL water. This solution was stirred at room temperature under an inert nitrogen atmosphere for 19h. At this time TLC analysis showed no evidence of starting material. The reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried and filtered. The solvent was then removed *in vacuo*. Spectral details as listed previously.



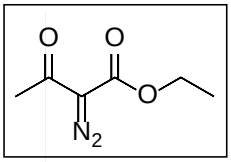
9 **11**

Entry	*Solvent*	*Volume*	*Time*	*Base*	*Conversion*[1]
1	Acetonitrile	5 mL	20h	DMAP	95%[2]
2	Acetonitrile	5 mL	20h	Et_3N	82%
3	Dichloromethane	5 mL	20.5h	DMAP	95%[2]
4	Dichloromethane	5 mL	20.5h	Et_3N	28%[2]
5	Water	5 mL	20h	DMAP	73%
6	Water	1.5 mL	20h	DMAP	93%
7	Water	5 mL	20h	Et_3N	55%
8	Water	1.5 mL	20h	Et_3N	98%
9	Ethanol	5 mL	21h	DMAP	74%[2]
10	Ethanol	5 mL	21h	Et_3N	74%
11	Acetonitrile	5 mL	20h	K_2CO_3	100%
12	Water	5 mL	20h	K_2CO_3	18%
13	Water	1.5 mL	20h	K_2CO_3	18%
14	Water	20 mL	20h	K_2CO_3	20%

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

[2] Unknown impurity (5%) with ethyl peaks at 1.4 ppm (t) and 4.4 ppm (q). Impurity not recovered following column chromatography on silica gel.

2.3.4 Investigation of effects of dilution and base loading

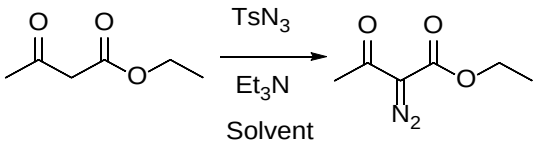


Representative procedure for reactions carried out in acetonitrile

A solution of tosyl azide **1** (0.16 g, 0.80 mmol) in 0.5 mL acetonitrile was added to a stirring solution of ethyl acetoacetate **9** (0.11 g, 0.79 mmol) and triethylamine (5.6 µL, 40 µmol, 5 mol%) in 1 mL acetonitrile. This solution was stirred at room temperature under an inert nitrogen atmosphere for 19h. At this time TLC analysis showed no evidence of starting material. The solvent was then removed *in vacuo* in order to obtain a ^{1}H NMR spectrum. Spectral details as listed previously.

Representative procedure for reactions carried out in water

A solution of tosyl azide **1** (0.17 g, 0.88 mmol) in 1 mL water was added to a stirring solution of ethyl acetoacetate **9** (0.11 g, 0.88 mmol) and triethylamine (18.4 µL, 131.7 µmol, 15 mol%) in 4 mL water. This solution was stirred at room temperature under an inert nitrogen atmosphere for 20h. At this time TLC analysis showed no evidence of starting material. The reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried and filtered. The solvent was then removed *in vacuo*. Spectral details as listed previously.

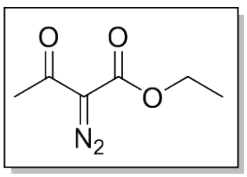


9 **11**

Entry	*Solvent*	*Dilution*	*Time*	*Base Loading*	*Concentration*	*Conversion*[1]
1	CH_3CN	1.5mL	19h	5mol%	0.60 mol/L	98%
2	CH_3CN	5mL	20h	5mol%	0.15 mol/L	82%
3	CH_3CN	1.5mL	19h	15mol%	0.53 mol/L	100%
4	CH_3CN	5mL	20h	15mol%	0.16 mol/L	98%
5	H_2O	1.5mL	19h	5mol%	0.56 mol/L	94%
6	H_2O	5mL	17h	5mol%	0.17 mol/L	11%
7	H_2O	1.5mL	19h	15mol%	0.57 mol/L	96%
8	H_2O	5mL	20h	15mol%	0.18 mol/L	74%

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

2.3.5 Investigation into critical reaction parameters (base loading, time, solvent)



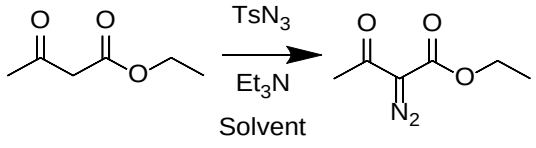
Representative procedure for reactions carried out in water

A solution of tosyl azide **1** (0.16 g, 0.79 mmol) in 0.5 mL water was added to a stirring solution of ethyl acetoacetate **9** (0.10 g, 0.79 mmol) and triethylamine (5.5 µL, 39.5 µmol, 5 mol%) in 1 mL water. This solution was stirred at room temperature under an inert nitrogen atmosphere for 19h. At this time TLC analysis showed no evidence of starting material. The

reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried and filtered. The solvent was then removed *in vacuo*. Spectral details as listed previously.

Representative procedure for reactions carried out in acetonitrile

A solution of tosyl azide **1** (0.18 g, 0.89 mmol) in 0.5 mL acetonitrile was added to a stirring solution of ethyl acetoacetate **9** (0.12 g, 0.89 mmol) and triethylamine (6.2 µL, 44.6 µmol, 5 mol%) in 1 mL acetonitrile. This solution was stirred at room temperature under an inert nitrogen atmosphere for 19h. At this time TLC analysis showed no evidence of starting material, and the solvent was removed *in vacuo*. Spectral details as listed previously.



9 **11**

Entry	*Solvent*	*Volume*	*Concentration*	*Time*	*Base Loading*	*Conversion* [1]
1	H_2O	1.5 mL	0.56 mol/L	19h	5 mol%	94%
2	H_2O	1.5 mL	0.57 mol/L	19h	15 mol%	96%
3	CH_3CN	1.5 mL	0.59 mol/L	19h	5 mol%	98%
4	CH_3CN	1.5 mL	0.53 mol/L	19h	15 mol%	100%
5	H_2O	1.5 mL	0.57 mol/L	5h	5 mol%	92%[2]
6	H_2O	1.5 mL	0.56 mol/L	5h	15 mol%	92%[2]
7	CH_3CN	1.5 mL	0.55 mol/L	5h	5 mol%	98%
8	CH_3CN	1.5 mL	0.55 mol/L	5h	15 mol%	100%

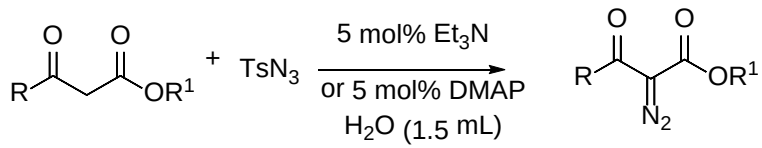
[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

[2] 100% of starting material consumed. Unknown impurity with ethyl peaks at 1.4 ppm (t) and 4.4 ppm (q). Impurity not recovered following column chromatography on silica gel.

2.3.6 Diazo transfer in water using 5 mol% of base – substrate scope

Representative procedure

p-Toluenesulfonyl azide **1** (0.210 g, 1.22 mmol, 1 equiv.) in 0.5mL water was added to a stirring solution of *t*-butyl acetoacetate **23** (0.241 g, 1.22 mmol, 1 equiv.) and DMAP (7.5 mg, 0.06 mmol, 5 mol %) in water (1.0 mL). The reaction was stirred under an inert nitrogen atmosphere at room temperature for 18 h until TLC showed no further evidence of starting material. Evidence for successful diazo-transfer could be seen from the presence of the white sulfonyl amide side product in the reaction mixture. The crude reaction mixture was extracted into ethyl acetate (2 x 15 mL). The ethyl acetate was then removed *in vacuo* and a ^{1}H NMR spectrum was obtained. The residue was re-dissolved in ethyl acetate and was then washed with 9 % KOH (2 x 30 mL), H_2O (30 mL), dried ($MgSO_4$) and concentrated to a yellow oil **12** (0.198 g, 80 %). Spectral details are consistent with those reported above. 9% KOH wash did not remove 100% of the sulfonyl amide by-product from the reactions done in water. Analytically pure samples could be obtained in this case by flash chromatography using ethyl acetate/hexane 30:70 as eluent.

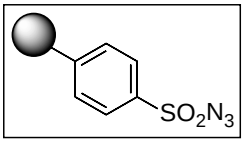


Entry	*R*	*R[1]*	*Diazo Product*	*Base (5 mol%)*	*% Conversion[1]*	*% Yield after KOH wash [2]*	*% Purity*	*% Yield [3]*
1	Me	*t*-Butyl	**12**	Et_3N	99	81	90	51
2	Me	*t*-Butyl	**12**	DMAP	95	80	87	50
3	Me	Pentyl	**13**	Et_3N	98	94	95	60
4	Me	Pentyl	**13**	DMAP	98	88	89	62
5	Me	2-Ethylbutyl	**16**	Et_3N	100	73	80	50
6	Me	2-Ethylbutyl	**16**	DMAP	98	86	95	58
7	Me	3,7-dimethyloct-6-enyl	**18**	Et_3N	93	82	88	52
8	Me	3,7-dimethyloct-6-enyl	**18**	DMAP	93	79	93	54
9	Me	Undec-10-en-1-yl	**17**	Et_3N	91	92	73	66
10	Me	Undec-10-en-1-yl	**17**	DMAP	91	86	91	60
11	*n*-Propyl	Et	**15**	Et_3N	84	89	88	61
12	*n*-Propyl	Et	**15**	DMAP	93	88	90	64

[1] % Conversion calculated from appropriate peak with key signal change in the ^{1}H NMR spectrum between starting material and product. [2] This yield reflects a synthetically pure sample. The % purity is reported in the following column. A ^{1}H NMR spectrum was obtained after the reaction mixture had been re-dissolved in EtOAC, washed with 3 x 15 mL 9% KOH solution, followed by 1 x 15 mL H_2O. The EtOAc layers were then combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. [3] Yield of analytically pure samples that were obtained by purification using column chromatography on silica gel.

2.4 Diazo transfer using polymer-supported azide

2.4.1 Synthesis of polystyrene-supported benzenesulfonyl azide [100-200 mesh, 1.5-2.0 mmol/g]



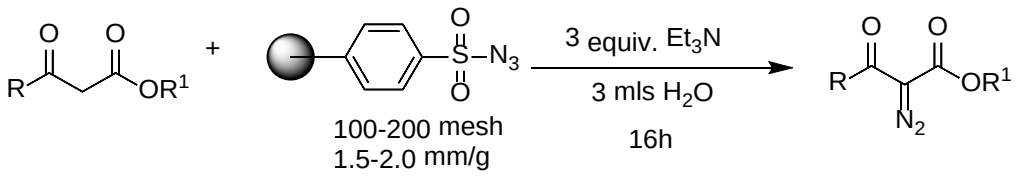
Polystyrene-supported benzenesulfonyl azide 25

Polystyrene-supported benzenesulfonyl chloride (100-200 mesh, 1.5-2.0 mmol/g) **26** (2.0 g) was 'swollen' by stirring in dimethylformamide (5.0 mL) for 5 min at room temperature. Sodium azide (0.39 g, 6 mmol), dissolved in water (1.0 mL) and diluted with DMF (7.0 mL), was added dropwise to produce an orange coloured solution. The reaction was stirred overnight at room temperature. The polymer-supported benzenesulfonyl azide **25** was isolated by gravity filtration using a fluted filter paper and washed with water (5 x 5 mL), dimethylformamide (5 x 5 mL) and dichloromethane (5 x 5 mL). The polystyrene-supported benzenesulfonyl azide resin **25** was spread on a clock-glass to dry. The product was weighed (2.04 g) and stored in a sample vial in the fridge. ν_{max}(ATR)/cm^{-1} 2125.

2.4.2 Diazo-transfer reactions using polystyrene-supported benzenesulfonyl azide– substrate scope

Representative procedure

Polystyrene benzenesulfonyl azide **25** (500 mg, 0.75 mmol) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester, *t*-butyl acetoacetate **23** (79 mg, 0.5 mmol) and triethylamine (0.22 mL, 1.5 mmol, 3 eq.) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give *t*-butyl 2-diazo-3-oxobutanoate **12** as a yellow oil (56 mg, 65 %). Spectral details are consistent with those reported above.



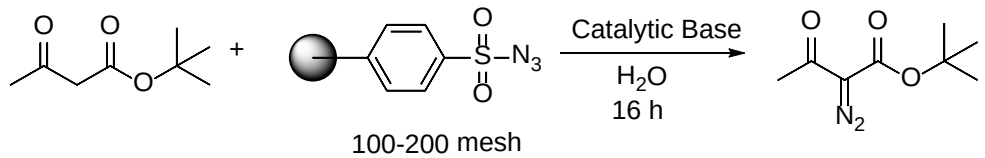
Entry	*R*	R^1	% Conversion	% Yield
1	Me	*t*-Butyl	100	65
2	Me	Pentyl	100	71
3	Me	2-Ethylbutyl	100	74
4	Me	3,7-Dimethyloct-6-enyl	100	77
5	Me	Undec-10-en-1-yl	100	70
6	*n*-Propyl	Et	96[1]	70

[1] 100% of starting material consumed. Unknown impurity with peaks at 3.0 ppm (t) and 4.4 ppm (q). Quantity estimated at <5%.

2.4.3 Diazo-transfer reactions using polystyrene-supported benzenesulfonyl azide and catalytic base loading

Representative Procedure, 3 equivalents Et_3N

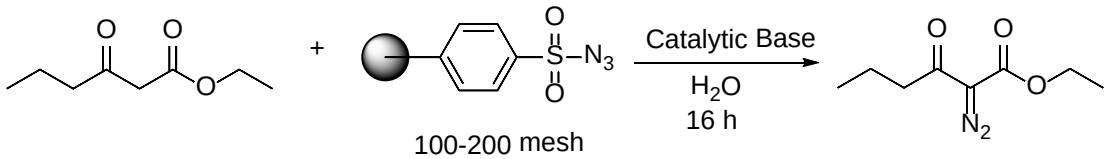
Polystyrene benzenesulfonyl azide **25** (500 mg, 0.75 mmol) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester, *t*-butyl acetoacetate **23** (79 mg, 0.5 mmol) and triethylamine (0.017 mL, 0.125 mmol, 0.25 eq.) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. A ^1H NMR spectrum of the crude reaction mixture was obtained. Spectral details are consistent with those reported above.



23 **12**

		Base Loading		
Base	Diazo Product	18 mol%	20 mol%	25 mol%
DMAP	**12**	74	95	36
Et_3N	**12**	91	97	94

Table shows % conversions.



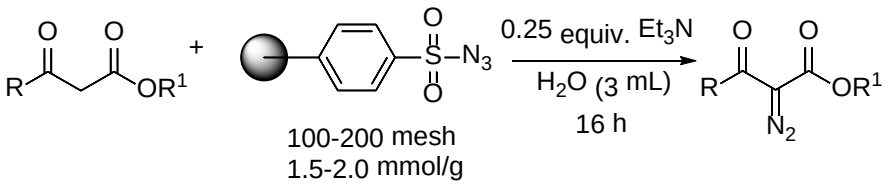
29 **15**

		Base Loading		
Base	Diazo Product	18 mol%	20 mol%	25 mol%
DMAP	**15**	70	33	61
Et_3N	**15**	32	83	91

Table shows % conversions.

Representative Procedure, 0.25 equivalents Et_3N

Polystyrene benzenesulfonyl azide **25** (500 mg, 0.75 mmol) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester, *t*-butyl acetoacetate **23** (79 mg, 0.5 mmol) and triethylamine (0.017 mL, 0.125 mmol, 0.25 eq.) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. A ^1H NMR spectrum of the crude reaction mixture was obtained. Spectral details are consistent with those reported above.



Entry	*R*	*R^1*	*Diazo product*	*Conversion (%)*
1	Me	*t*-Butyl	**12**	94
2	Me	Pentyl	**13**	97
3	Me	2-Ethylbutyl	**16**	94
4	Me	3,7-dimethyloct-6-enyl	**18**	65
5	Me	Undec-10-en-1-yl	**17**	69
6	*n*-Propyl	Et	**15**	91

2.5 Synthesis of polymer-supported benzenesulfonyl azide

2.5.1 1st generation synthesis of benzenesulfonyl azide

30 **26**

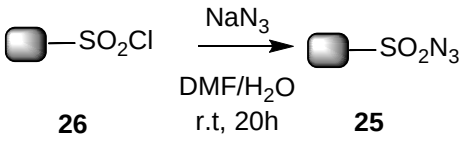
Amberlyst® 15 **30** (1 g, 4.5 mmol) was reacted with 10 equivalents of thionyl chloride (5.35 g, 45 mmol) in the presence of an excess of triethylamine (1.26 mL, 9 mmol) in dimethylformamide (15 mL). The reaction mixture was allowed to stir overnight, before being isolated by suction filtration and washed with several 5 mL aliquots of dichloromethane. The resulting beads were brown in colour (1.22 g) and were allowed to dry overnight, before being stored in the fridge.

Note: A large batch of the polymer-supported benzenesulfonyl chloride **26** was required for tests and for carrying forward to form the polymer-supported benzenesulfonyl azide. However when the reaction was carried out on the larger scale, large amounts of a yellow/brown powder remained in the Buchner with the beads. While this powder had been observed in the small scale reaction, several washes with DCM removed it, however this did

not apply on the larger scale. A sample of the powder was taken, and some solubility tests were carried out. It was found that hot acetonitrile dissolved this unknown solid. Several washes with hot acetonitrile through the Buchner funnel removed approximately half of the powder initially observed.

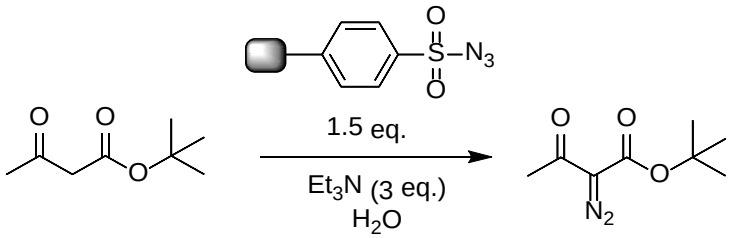
The mixture of beads and powder was then placed in an Omnifit glass column and using a pump, acetonitrile was pumped through the column at 70° C at a rate of 2.5 mL/min. After approximately 30 mins, it was observed that the column no longer appeared to contain any powder, and the waste beaker contained particulate matter. The rest of the beads were also purified in this manner.

2.5.1.1 Reaction with sodium azide



Polystyrene-supported benzenesulfonyl chloride **26** (2.03 g, 9.13 mmol) was 'swollen' by stirring in dimethylformamide (10 mL) for 5 min at room temperature. Sodium azide (0.89 g, 13.69 mmol, 1.5 eq.), dissolved in water (2 mL) and diluted with DMF (14 mL), was added dropwise to produce an orange coloured solution. The reaction was stirred overnight at room temperature. The polymer-supported benzenesulfonyl azide **25** was isolated by gravity filtration using a fluted filter paper and washed with water (5 x 5 mL), dimethylformamide (5 x 5 mL) and dichloromethane (5 x 5 mL). The polystyrene-supported benzenesulfonyl azide resin **25** was spread on a clock-glass to dry. The product was stored in a sample vial in the fridge (1.96 g). ν_{max}(ATR)/cm^{-1} 2136.

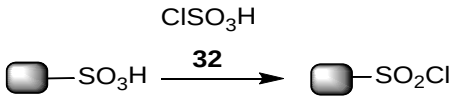
2.5.1.2 Use of synthetic polymer-supported benzenesulfonyl azide



23 **12**

Polystyrene benzenesulfonyl azide **25** (160 mg, 0.75 mmol, 1.5 equivalents) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester, *t*-butyl acetoacetate (79 mg, 0.5 mmol) and triethylamine (0.22 mL, 1.5 mmol, 3 equivalents) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give *t*-butyl 2-diazo-3-oxobutanoate **12** as a yellow oil. A ^1H NMR spectrum of the crude reaction mixture showed 36% conversion to the desired product, however there were additional singlets at 1.48 and 2.38 ppm that correspond to an unknown impurity.

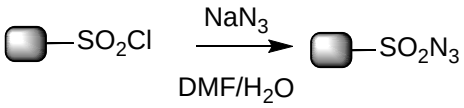
2.5.2 2nd generation synthesis of benzenesulfonyl azide



30 **26**

Amberlyst® 15 **30** (10.7 g, loading 4.5 mmol/g, 48.15 mmol) was placed in a round bottomed flask. Chlorosulfonic acid **32** (20 mL, 0.30 mol) was added and the resulting slurry was heated at 70C for 1 h under an inert atmosphere.[17] Once cooled to room temperature, dichloromethane (50 mL) was added and the resin was filtered, washed with several portions of dichloromethane (150 mL) and then with a mixture of THF : dichloromethane (1:9, 100 mL). The resulting beads were dark brown in colour and were allowed to dry overnight in a $CaCl_2$ dessicator, before being stored in the fridge.

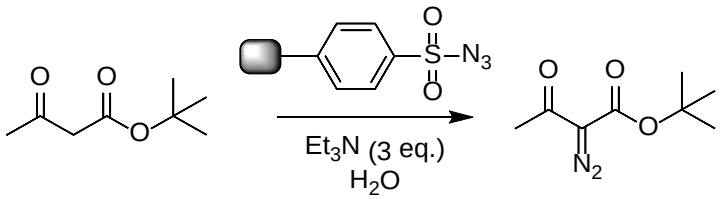
2.5.2.1 Reaction with sodium azide



26 **25**

Polystyrene-supported benzenesulfonyl chloride **26** (17.49 g, 78.69 mmol) was 'swollen' by stirring in dimethylformamide (15 mL) for 5 min at room temperature. Sodium azide (10.23 g, 157.39 mmol), dissolved in water (15 mL) and diluted with DMF (20 mL), was added dropwise to produce an orange coloured solution. The reaction was stirred overnight at room temperature. The polymer-supported benzenesulfonyl azide **25** was isolated by gravity filtration using a fluted filter paper and washed with water (5 x 5 mL), dimethylformamide (5 x 5 mL) and dichloromethane (5 x 5 mL). The polystyrene-supported benzenesulfonyl azide resin **25** was spread on a clock-glass to dry. The product was stored in a sample vial in the fridge. ν_{max}(ATR)/cm^{-1} 2130.

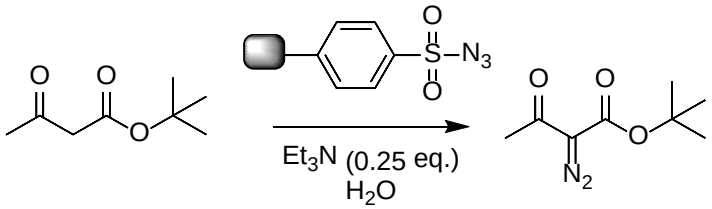
2.5.2.2 Use of synthetic polymer-supported benzenesulfonyl azide



23 **12**

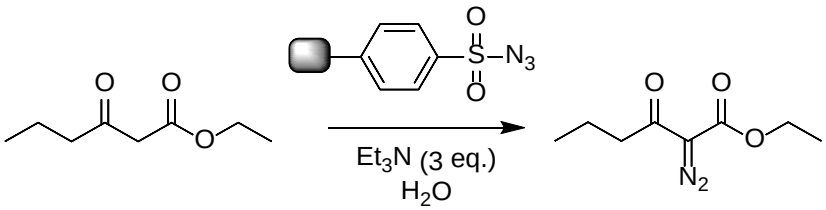
Polystyrene-supported benzenesulfonyl azide **25** (0.33 g, 1.5 mmol, 1.5 eq.) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester, *t*-butyl acetoacetate **23** (158 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give *t*-butyl 2-diazo-3-oxobutanoate **12** as a yellow

oil. A ^{1}H NMR spectrum of the crude reaction mixture showed 100% conversion to the desired product.



23 **12**

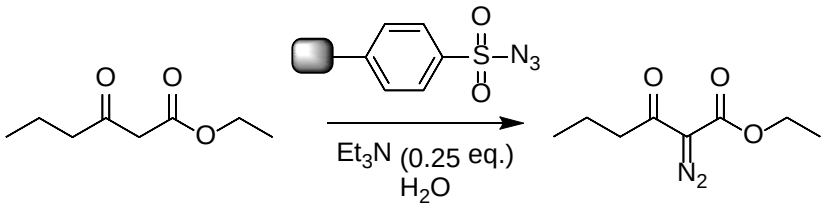
Polystyrene benzenesulfonyl azide **25** (0.33 g, 1.5 mmol, 1.5 eq.) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester *t*-butyl acetoacetate **23** (158 mg, 1 mmol) and triethylamine (34.9 µL, 0.25 mmol) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give *t*-butyl 2-diazo-3-oxobutanoate **12** as a yellow oil. A ^{1}H NMR spectrum of the crude reaction mixture showed no reaction had occurred.



29 **15**

Polystyrene benzenesulfonyl azide **25** (0.33 g, 1.5 mmol, 1.5 eq.) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester, *n*-propyl acetoacetate **29** (158 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated

by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give *n*-propyl 2-diazo-3-oxobutanoate **15** as a yellow oil. A ^1H NMR spectrum of the crude reaction mixture showed complete consumption of the ester starting material, however in addition to *n*-propyl 2-diazo-3-oxobutanoate **15**, evidence was seen in the spectrum for ~10% of an unknown impurity which was not recovered following column chromatography on silica gel.



29 **15**

Polystyrene benzenesulfonyl azide **25** (0.33 g, 1.5 mmol, 1.5 eq.) was placed in a round bottomed flask with 1.5 mL H_2O and stirred at room temperature for 5 min. A mixture of the ester, *n*-propyl acetoacetate **29** (158 mg, 1 mmol) and triethylamine (34.9 µL, 0.25 mmol) in 1.5 mL H_2O was added dropwise. The reaction was stirred at room temperature for 16 h. The resin was removed by gravity filtration and the organic layer was extracted into ether (15 mL). The resin was re-stirred in ether (5.0 mL) for 2 h at room temperature. The resin was isolated by filtration and both ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give *n*-propyl 2-diazo-3-oxobutanoate **15** as a yellow oil. A ^1H NMR spectrum of the crude reaction mixture showed 11% conversion to the desired product.

2.6 References

[1] R. H. Tale, R. N. Adude, *Tetrahedron Lett.* **2006**, *47*, 7263–7265.

[2] Kishimoto, Matsubara, *J. Chem. Soc. Japan* **1975**, 701–704.

[3] G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Tetrahedron* **1998**, *54*, 2843–2852.

[4] J. C. Shivers, M. L. Dillon, C. R. Hauser, *J. Am. Chem. Soc.* **1947**, *69*, 119–123.

[5] S. Hazen, G. G.; Bollinger, F. W.; Roberts, F. E.; Russ, W. K.; Seman, J. J.; Staskiewicz, *J. Org. Synth.* **1995**, *73*, 144.

[6] F. W. Bollinger, L. D. Tuma, *Synlett* **1996**, 407–413.

[7] M. Regitz, G. Maas, *Diazo Compounds. Properties and Synthesis.*, Academic Press, Orlando **1986**.

[8] T. J. Curphey, *Org. Prep. Proced. Int.* **1981**, *13*, 112–115.

[9] M. Kitamura, N. Tashiro, S. Miyagawa, T. Okauchi, *Synthesis* **2011**, 1037–1044.

[10] A. M. Harned, W. M. Sherrill, D. L. Flynn, P. R. Hanson, *Tetrahedron* **2005**, *61*, 12093–12099.

[11] E. Tarrant, New Insights into the Synthesis of α-Diazocarbonyl Compounds and Their Decomposition Pathways, PhD Thesis, University College Cork, **2012**.

[12] S. V Galiullina, V. M. Zakharova, G. P. Kantin, V. A. Nikolaev, *Russ. J. Org. Chem.* **2007**, *43*, 607–614.

[13] M. E. Meyer, E. M. Ferreira, B. M. Stoltz, *Chem. Commun.* **2006**, 1316–1318.

[14] T. O. Mitsuru Kitamura, Norifumi Tashiro, Satoshi Miyagawa, *Synthesis* **2011**, *7*, 1037-1044.

[15] R. M. Moriarty, B. R. Bailey III, O. Prakash, I. Prakash, *J. Am. Chem. Soc.* **1985**, *107*, 1375–1378.

[16] D. B. Ramachary, V. V Narayana, K. Ramakumar, *Tetrahedron Lett.* **2008**, *49*, 2704–2709.

[17] S. M. Nicolle, C. J. Hayes, C. J. Moody, *Chem. - A Eur. J.* **2015**, *21*, 4576–4579.

Chapter 3

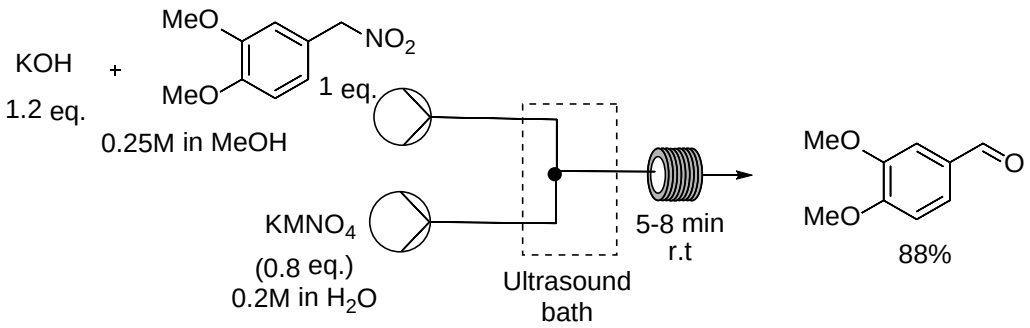
Results and Discussion

Table of Contents

3.1 Background

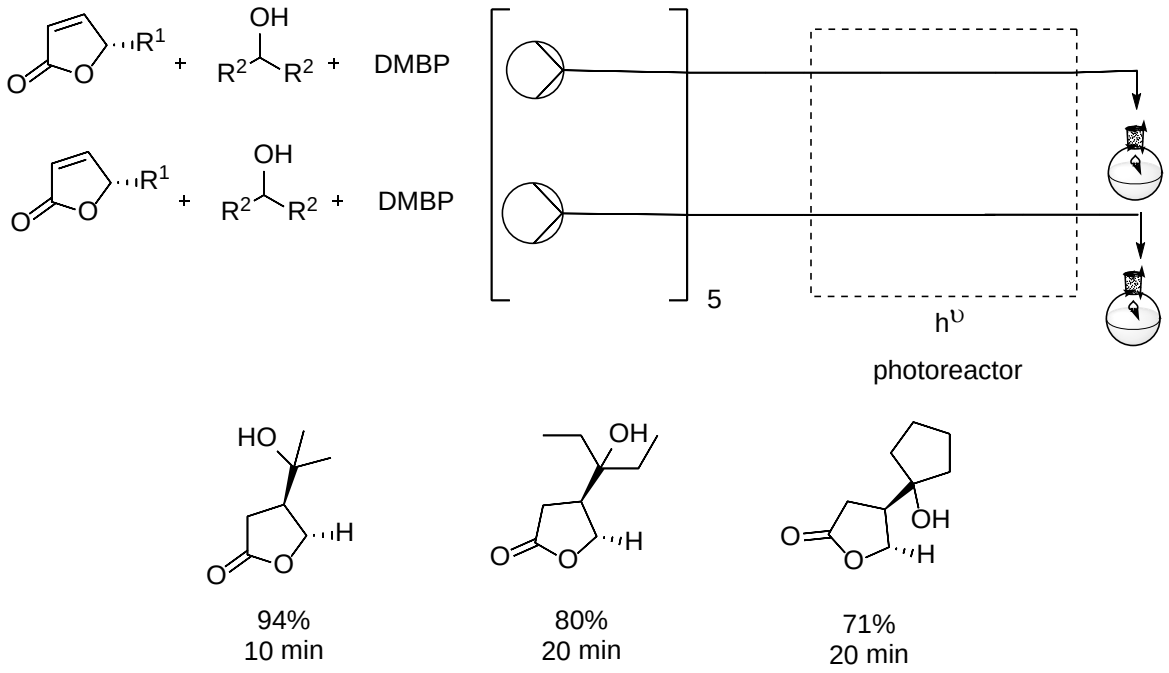
Flow chemistry has experienced a surge in popularity in recent years, and has many benefits to offer over traditional batch synthesis. Numerous reviews exist in the literature on the advantages and limitations of flow chemistry.[1–11] Some of the many advantages of flow chemistry include enhanced control of heat and mass transfer, increased capacity to run serial reactions as well as high reproducibility and ease of scale up.[7] Perhaps the principal appeal of continuous processing is the increased safety profile associated with it in comparison to batch chemistry, afforded by the 'make and use' concept which it utilises.[4] This means that chemicals which are dangerous, volatile or toxic may be generated and used *in situ*, without exposure of the operator to hazardous intermediates. This also negates the need for concentrated solutions of dangerous reagents at any one time.

With these advantages in mind, many groups have sought new methods of carrying out established chemistry in cleaner, safer more efficient ways using continuous processing. Continuous flow set-ups using syringe pumps, as well as commercially available flow reactors may be adapted to incorporate in-line monitoring or alternative reactor modules. Ley and co-workers reported the use of an ultrasound bath to prevent blockages when processing slurries as part of a potassium permanganate mediated oxidation in flow, as illustrated in **Scheme 3.1**.[12]



Scheme 3.1

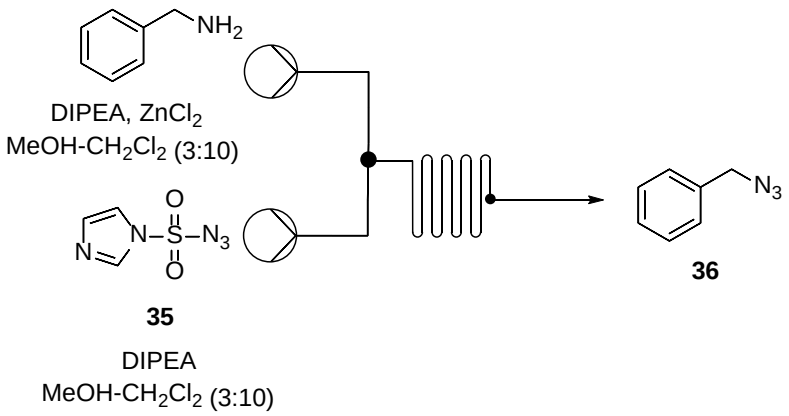
Nolan and Oelgemöller have reported the use of an in-line photoreactor.[13,14] Most recently, photoadditions involving 2(5*H*)-furanones were achieved in good to excellent yields in very short reaction times, using a custom-built multimicrocapillary flow reactor, as shown in **Scheme 3.2**.[15] This system allows up to 10 simultaneous reactions, and uses 4,4-dimethoxybenzophenone (DMBP) as a photosensitiser.



Scheme 3.2

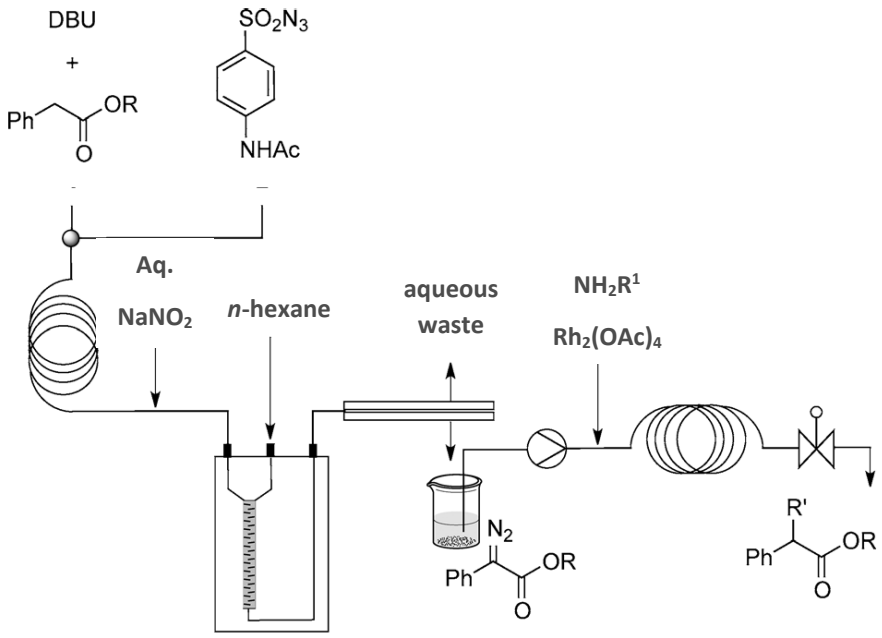
Several examples have been reported of the synthesis of hazardous intermediates such as diazonium salts,[16–24] and diazo compounds,[16,25–29] using continuous processing in the literature, many of which have previously been discussed in **Section 1.4**. However few examples exist in the literature of diazo transfer reactions in flow. The first reported diazo transfer carried out using continuous processing was reported by workers at GlaxoSmithKline,[30] where 2,4,6-triisopropylbenzenesulfonyl azide was used to transfer a diazo group to ethyl acetoacetate **9** in a segmented flow system.

Rutjes *et al*. prepared organic azides by diazo transfer to the corresponding benzyl amines with imidazole-1-sulfonyl azide **35** (**Scheme 3.3**).[31] The authors used this method to generate 1 g/h of benzyl azide **36** using a single flow reactor.



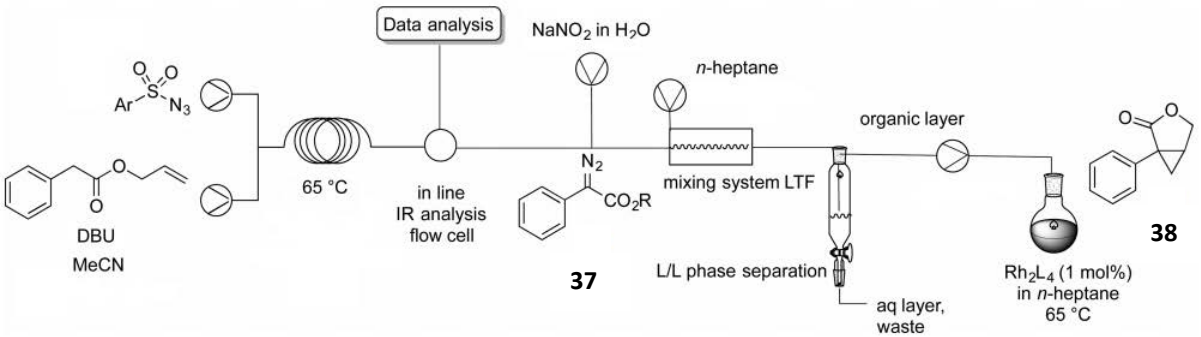
Scheme 3.3

Wirth and co-workers first published a continuous process for the safe generation and use of carbenes *via* diazo transfer.[32] The authors achieved successful diazo transfer to a range of phenylacetates, and then decomposed the compounds in the presence of rhodium(II) catalysts. Isolation of the diazo compounds was neatly avoided by use of a specially designed in-line liquid-liquid extraction, as shown in **Scheme 3.4**.



Scheme 3.4 Reproduced from Ref. 32.

The authors subsequently reported use of this same in-line liquid-liquid extraction in their telescoped semi-batch synthesis of bicyclic lactones, as illustrated in **Scheme 3.5**.[33] Diazo transfer was achieved by combining the substrate and the diazo transfer reagent at a T-piece. The formation of the diazo compound **37** was confirmed by in-line IR monitoring before purification is by liquid-liquid separation. A stream of the diazo compound in the organic layer is then directed into a batch reactor containing the catalyst in order to furnish the bicyclic lactone **38**.



Scheme 3.5 Reproduced from Ref 33.

Use of continuous processing for diazo transfer reactions overcomes many of the issues associated with performance of these transformations on an industrial scale. Conventional diazo transfer methods are far from ideal for use in industry, due to the safety hazards associated with the diazo transfer reagents,[34,35] as well as the exothermic reaction which takes place during the transfer of the diazo group and the potential for runaway reactions which this represents on a large scale.[32] As discussed in **Section 1.2.2**, although newer, safer diazo transfer reagents have been extensively reported,[36–40] a reagent has yet been found to be as effective as *p*-toluenesulfonyl azide **1**.

If efficient diazo transfer with alternative reagents is not a viable route for the preparation of these reactive intermediates, then use of *p*-toluenesulfonyl azide **1** in the controlled environment of a continuous process is the best option available.

3.2 Initial investigation into diazo transfer using flow reactor

The aim of this project was initially to develop a greener methodology for diazo transfer. When the opportunity to expand this research to include synthesis in flow it was viewed as a perfect extension to the work outlined in Chapter 2. Use of a flow reactor allowed us to further improve the environmental and safety aspects of our new approach to diazo transfer, by exploiting the increased safety profile of these systems for the use of *p*-toluenesulfonyl azide **1**.

A Vapourtec R-series flow reactor was used to perform all continuous processes in the course of this project, as illustrated in **Figure 3.1**. This flow machine consists of four pumps and may be used with up to four temperature controlled tubular reactors. The reactor has working flow rates of 0.05 mL/min up to 9.99 mL/min, and a working temperature range of -70 °C to 250 °C. PFA tubing with an internal diameter of 1mm is used throughout, including in the 10 mL tubular reactors used for this project.

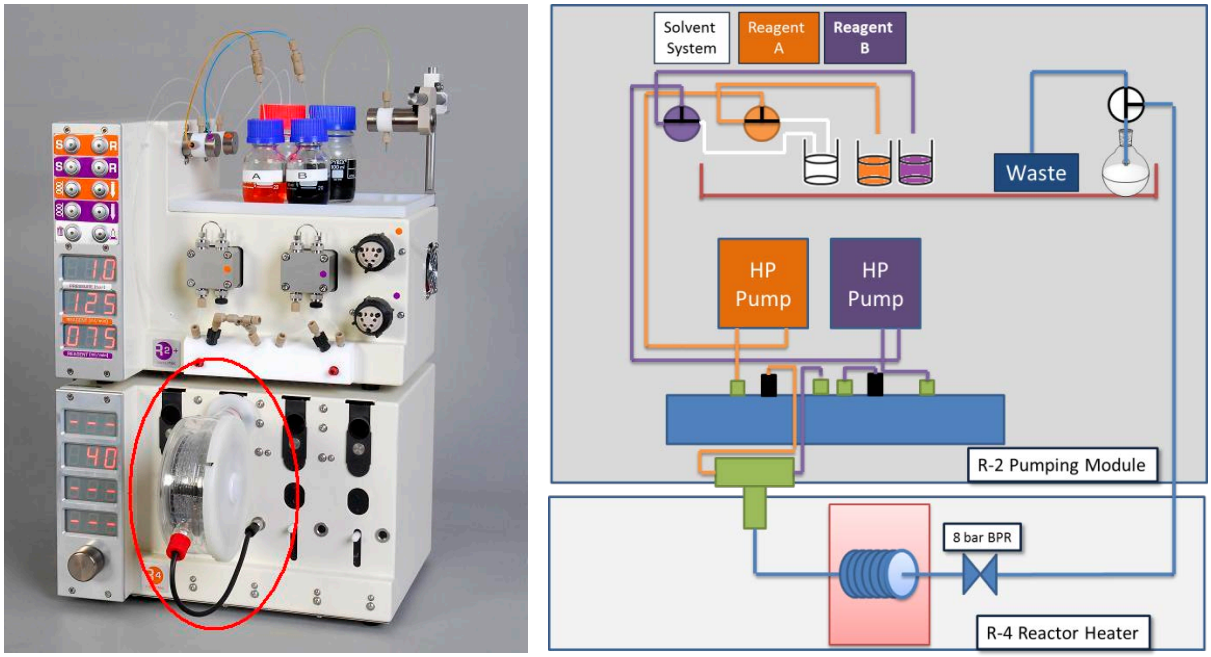
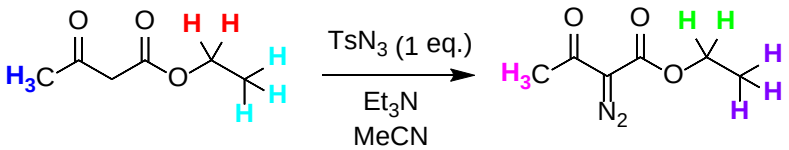


Figure 3.1 Vapourtec R-Series reactor and corresponding general schematic diagram. Reproduced with permission from Vapourtec®.

The initial experimental conditions to be employed were one equivalent of β-ketoester, with one equivalent of base and *p*-toluenesulfonyl azide **1** in water. Ethyl acetoacetate **9** was chosen as a good model substrate, due to the distinct differences in chemical shifts in the ^{1}H NMR spectrum between the CH_2 of the ethyl ester side chain and the CH_3 of the methyl ketone in the starting material and product (**Scheme 3.6**).



9

- 2.3 ppm, 3H, s
- 4.2 ppm, 2H q
- 1.3 ppm, 3H t

11

- 2.5 ppm, 3H, s
- 4.3 ppm, 2H q
- 1.3 ppm, 3H t

Scheme 3.6

It was decided to carry out the reaction at 0.5M concentration as an initial starting point, therefore 1M solutions of each reagent were required. A 1M solution of ethyl acetoacetate **9** and triethylamine was made up in water, pre-forming the enolate in solution. However when preparation of a 1M solution of p-toluenesulfonyl azide **1** in water was attempted, it was found that the solution formed was not homogenous due to low solubility of **1** in water. A drawback associated with continuous processing is that all reagents and products should be soluble in the reaction solvent, so as to ensure efficient mixing and prevent precipitate clogging the lines, therefore leading to system failure from elevated pressure.[6]

Alternative 'green' solvents were therefore investigated. Reports by GlaxoSmithKline and the American Chemical Society Green Chemistry Institute were used to choose acetone, ethyl acetate and ethanol as alternative 'green' solvents to water.[41,42] As acetonitrile is the traditional choice of solvent for these reactions it was used as a standard to which other solvents could be compared. The solubility of *p*-toluenesulfonyl azide **1** in each of the alternative solvents was checked and was determined to give homogenous solutions in each.

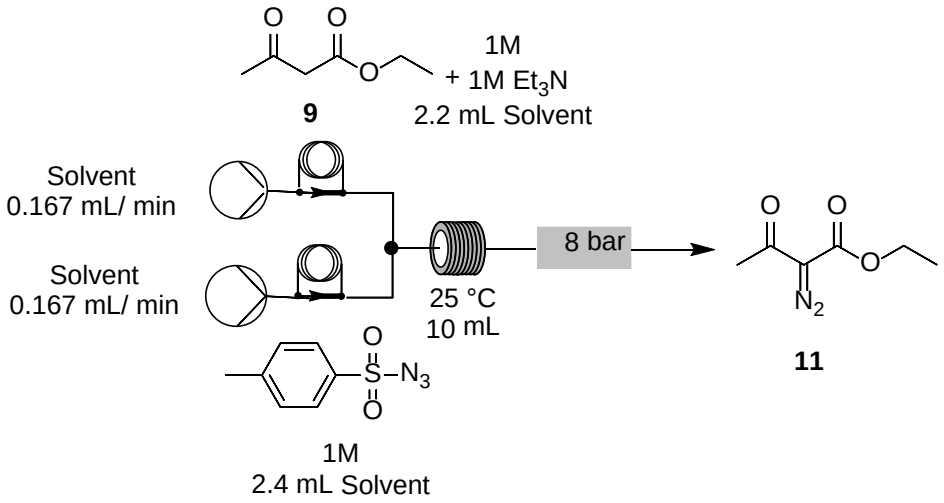
The diazo transfer reactions were carried out with a 30 minute residence time and a flow rate of 0.333 mL/min as determined by the 10mL reactor volume. The flow rate is determined by the following formula:

$$\text{Residence Time} = \text{Volume} / \text{Flow rate}$$

To achieve an overall flow rate of 0.333 mL/min, each pump is set to 0.167 mL/min. 2 mL sample loops were used to inject the samples into the reactor. The results are summarised in **Table 3.1**.

Similarly to the previous chapter, this is intended to be a high throughput study for determination of the optimal conditions to achieve greener diazo transfer using flow chemistry. In addition to this, the long-term aim for this research is to eventually prepare and react α-diazo-β-ketoesters without isolation in a telescoped reaction, to prepare a range of lactones and dioxinones (these syntheses will be discussed in detail in Chapter 4). Therefore, it was decided not to carry out chromatography on each sample to isolate non-novel compounds.

Table 3.1 ***Diazo Transfer in Flow with 1eq. triethylamine***

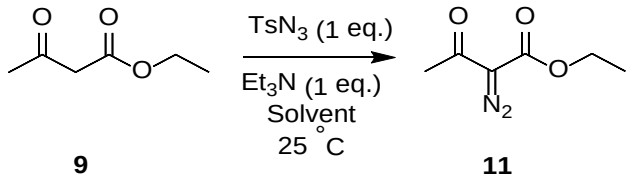


Entry	*Solvent*	*Residence Time (min)*	*Temperature (°C)*	*% Conversion[1]*
1	Acetone	30	25	76
2	Ethyl Acetate	30	25	66
3	Ethanol	30	25	96
4	Acetonitrile	30	25	68

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

As can be seen above, the best conversion from **9** to **11** was obtained when ethanol was used as the reaction solvent. The other solvents all resulted in very comparable conversions. These results were a great starting point, with good to excellent conversions achieved in only 30 minute reaction times. The corresponding batch reactions were also carried out for comparison purposes, the results of which are shown below in **Table 3.2**.

Table 3.2 ***Diazo Transfer in Batch with 1eq. triethylamine***



9 **11**

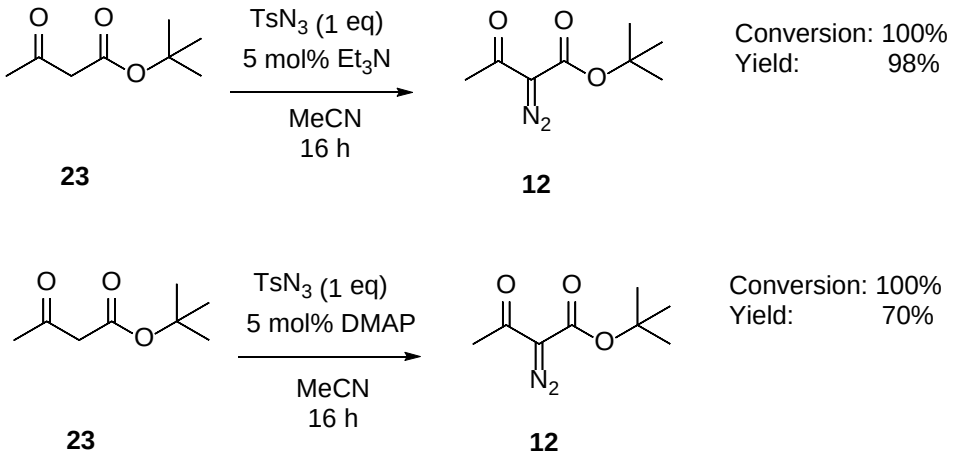
Entry	*Solvent*	*Reaction Time (min)*	*Temperature (°C)*	*% Conversion*[1]
1	Acetone	30	25	85
2	Ethyl Acetate	30	25	62
3	Ethanol	30	25	91
4	Acetonitrile	30	25	93

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

Surprisingly, diazo transfer in acetone and acetonitrile performed better under batch conditions than in continuous processing when one equivalent of base is employed, while conversions achieved in ethyl acetate are comparable using both methods. Therefore there is scope for improvement in the parameters employed for diazo transfer in the flow reactor. However, as the aim of this project is to employ our optimised 'greener' methodology for this reaction to a continuous process and following on from the catalytic studies outlined in Chapter 2, the base loading was reduced to 5 mol% for the next set of experiments. It was decided to eliminate ethyl acetate as a reaction solvent going forward as in addition to giving the poorest conversions of the solvents tested, the ^{1}H NMR spectra of the crude reaction mixtures obtained from reactions done in ethyl acetate showed that the samples were of poorer purity than those from reactions done in the other solvents.

3.3 Initial investigation into diazo transfer using flow reactor using catalytic amount of base

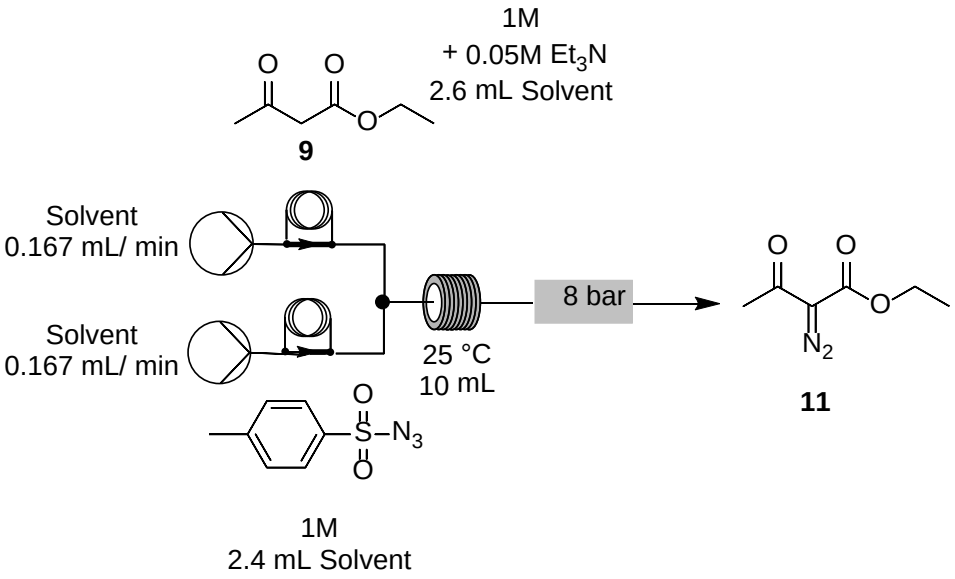
As previously outlined in Chapter 2, diazo transfer using sub-stoichiometric quantities of base has been successfully achieved in water, however very little investigation has been carried out using catalytic amounts of base in organic solvents. Two initial experiments were carried out previously within the group using 5 mol% base and *t*-butyl acetoacetate **23** in acetonitrile, as can be seen in **Scheme 3.7**.[43]



Scheme 3.7

While the initial aim of this work had been to achieve diazo transfer with catalytic quantities of base in water using continuous processing, the solubility issues discussed previously prevented this. Therefore substoichiometric base loading in organic solvent for diazo transfer was revisited. The reaction set-up was similar, using the same temperature (25 °C) and reactor volume (10 mL). A 1 M solution was made up with respect to ethyl acetoacetate **9**, requiring a slightly larger volume of solvent to compensate for the decreased volume of base in the solution. The results of these experiments are summarised in **Table 3.3**.

Table 3.3 ***Diazo Transfer in Flow with 5 mol% triethylamine***



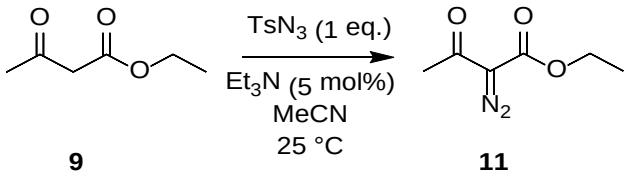
Entry	*Solvent*	*Base Loading*	*Residence Time (min)*	*Temperature (°C)*	*% Conversion*[1]
1	Acetone	5 mol%	30	25	30
2	Ethanol	5 mol%	30	25	41
3	Acetonitrile	5 mol%	30	25	39
4	Ethanol	25 mol%	30	25	95

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

As can be seen from Entries 1-3 above, ethanol again gave the highest conversion to the desired product. While the conversions were significantly lower than those achieved in **Table 3.1** above, achieving 41% conversion from **9** to **11** in only 30 minutes using 5 mol% of base is a good accomplishment. When a higher base loading was tested in ethanol, conversion was increased from 41% using 5 mol% triethylamine to 95% using 25 mol% triethylamine. This is comparable to the conversion of 96% achieved when a full equivalent of triethylamine was employed under the same conditions (**Table 3.1**, Entry 3).

The corresponding batch reactions were also carried out, the results of which are outlined in **Table 3.4**. When Entries 1 and 3 from **Tables 3.3 and 3.4** are compared, an improvement in conversion is observed when the reaction is done in flow compared to batch. However when the reaction is done in ethanol at the lower base loading of 5 mol%, the reaction is more efficient when done in batch compared to flow. In contrast, when diazo transfer was carried out in ethanol with 25 mol% of triethylamine in batch, a decrease in reactivity is observed when compared to the same reaction done in the flow reactor.

Table 3.4 ***Diazo Transfer in Batch with 5 mol% triethylamine***



9 **11**

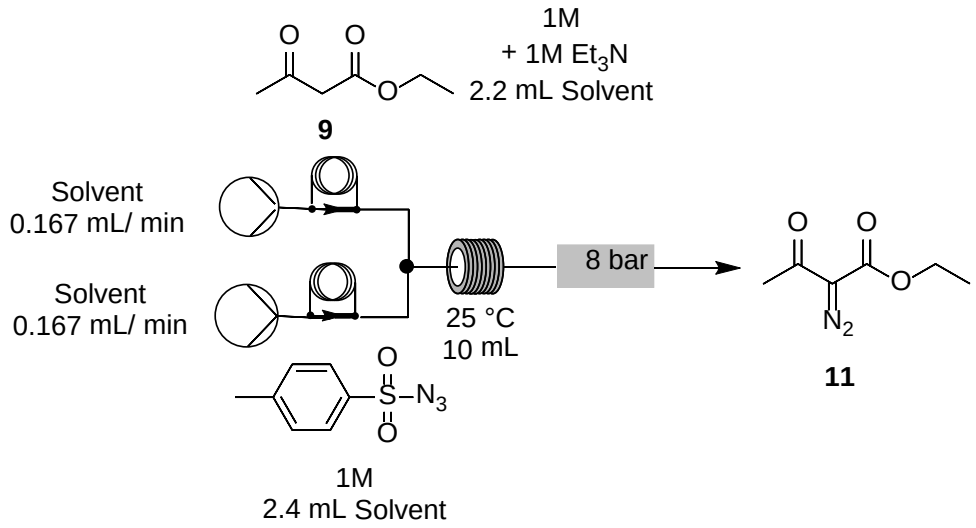
Entry	*Solvent*	*Base Loading*	*Reaction Time (min)*	*Temperature (°C)*	*% Conversion*
1	Acetone	5 mol%	30	25	22
2	Ethanol	5 mol%	30	25	56
3	Acetonitrile	5 mol%	30	25	33
4	Ethanol	25 mol%	30	25	84

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

3.4 Investigating effect of water on reaction efficiency

When the initial set of experiments were carried out, lab grade acetone was accidentally used in place of HPLC grade acetone for a diazo transfer reaction. This somewhat serendipitous mistake led to a very interesting result, as shown below in **Table 3.5**.

Table 3.5 ***Diazo Transfer in Flow with 1 equivalent of base in acetone***

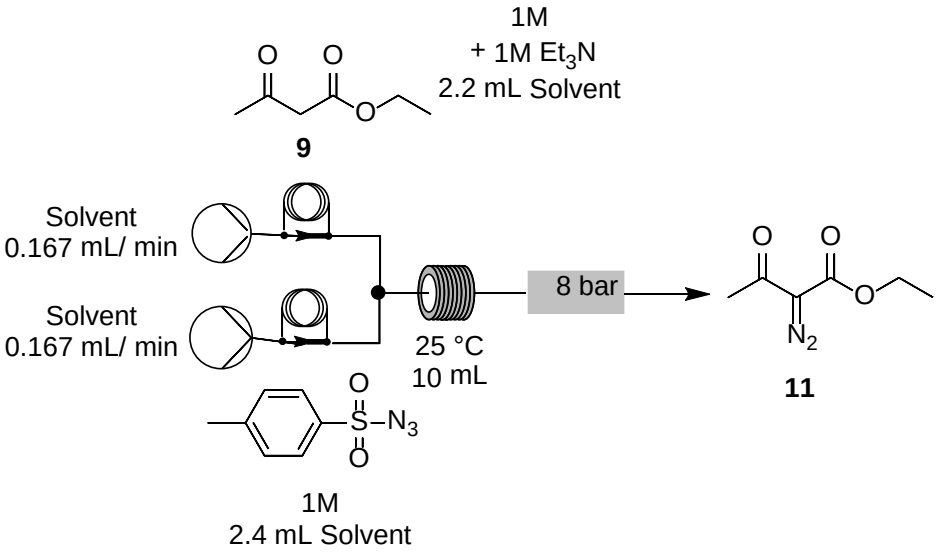


Entry	*Solvent*	*Residence Time (min)*	*Temperature (°C)*	*% Conversion*[1]
1	HPLC grade acetone	30	25	76
2	Lab grade acetone	30	25	93

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

When all other reaction conditions were unchanged, the use of lab grade acetone in place of HPLC grade acetone resulted in a 17% increase in conversion. It was hypothesized that this increase in reactivity could be due to the increased water content in the lower purity acetone. It was decided to examine the influence of adding a quantity of water to the reaction solvent on the efficacy of the diazo transfer reaction, the results of which are outlined in **Table 3.6**. This had the advantage of linking this methodology more closely with the batch protocol previously developed in Chapter 2, where water was used as the reaction solvent.

Table 3.6 ***Examining the effect of 5% water on the diazo transfer reaction in flow with 1eq. base***



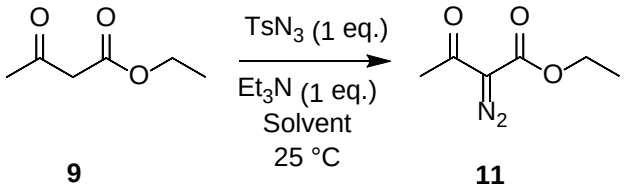
Entry	*Solvent*	*Ratio*	*Residence Time (min)*	*% Conversion*	*Table 3.1 % Conversion*
1	Acetone:H_2O	95:5	30	98	76
2	Ethyl Acetate:H_2O	95:5	30	100	66
3	Ethanol:H_2O	95:5	30	100	96
4	Acetonitrile:H_2O	95:5	30	98	68

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

We were delighted to see that by introducing 5% water to each solvent mixture, the conversions obtained were significantly improved. Improvements in conversion ranged from 22-34% when compared to results outlined in **Table 3.1**, except in the case of ethanol, which had already proved to be a very efficient reaction solvent. When the corresponding reactions were carried out in batch, the effect of adding water to the solution was much less striking

(**Table 3.7**). Except for the case of ethyl acetate (Entry 2) which showed a 22% increase in conversion, all other conversions were comparable in the presence or absence of water.

Table 3.7 ***Examining the effect of 5% water on the diazo transfer reaction in batch with 1eq. base***



9 **11**

Entry	***Solvent***	***Ratio***	***Reaction Time (min)***	***Temperature (°C)***	***% Conversion[1]***	***Table 3.2 % Conversions***
1	Acetone:H_2O	95:5	30	25	92	85
2	Ethyl Acetate:H_2O	95:5	30	25	84	62
3	Ethanol:H_2O	95:5	30	25	89	91
4	Acetonitrile:H_2O	95:5	30	25	93	93

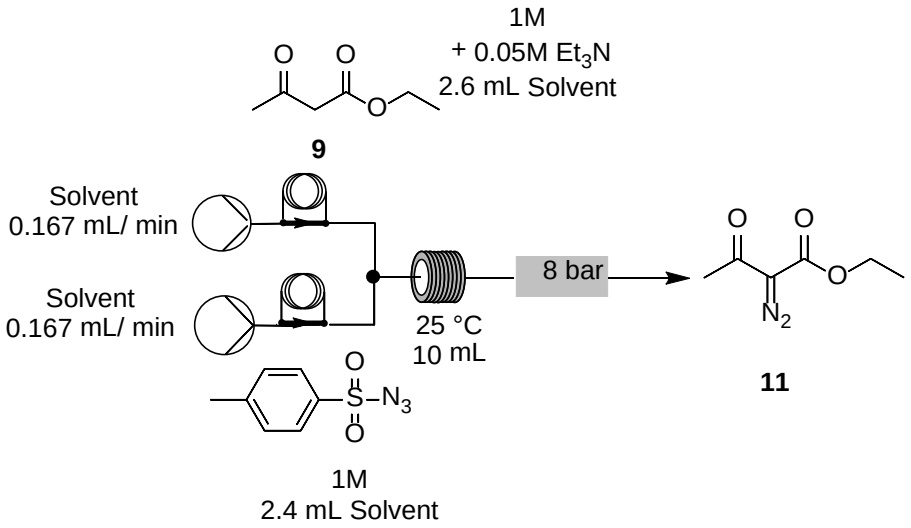
[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

This was a very encouraging result, as a key aim of this research is to determine the optimum conditions for greener diazo transfer using continuous processing. With this in mind, it was decided to combine studies outlined in **Table 3.4** and **Table 3.6** and carry out a series of reactions using 5 mol% of base in solvent containing 5% water.

3.5 Investigating effect of water on reaction efficiency – catalytic quantity of base

One of our main aims in developing a greener diazo transfer methodology was to reduce the base loading required for the reaction. As shown in **Section 3.3**, diazo transfer in flow with a catalytic quantity of base gave moderate yields. Significant improvements in conversion were observed in the previous section by addition of a small quantity of water to the solvent. It was hoped that employing these two concepts together would result in improved conversions with 5 mol% of base. The results of these experiments are outlined in **Table 3.8**.

Table 3.8 ***Examining the effect of 5% water on the diazo transfer reaction in flow with 5 mol% base***

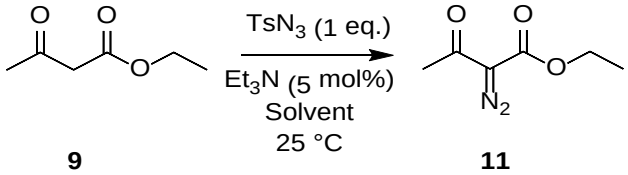


Entry	*Solvent*	*Ratio*	*Base Loading*	*Reaction Time (min)*	*% Conversion[1]*	*Table 3.3 % Conversion*
1	Acetone : H_2O	95:5	5 mol%	30	57	30
2	EtOH : H_2O	95:5	5 mol%	30	67	41
3	Acetonitrile : H_2O	95:5	5 mol%	30	46	39

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

Gratifyingly, a very positive effect was observed after the addition of 5% water to each solvent although the conversions were still low. Comparing the results obtained above to those recorded in **Table 3.3**, a large increase in conversion can be obtained by simply varying the solvent from acetone to 95:5 acetone-water. A 26% increase was observed when ethanol was changed for 95:5 ethanol-water. Interestingly, the effect was much less striking when acetonitrile was used with only a 7% increase in conversion. When the corresponding batch reactions were carried out, as summarised in **Table 3.9** below, a similar outcome was observed, with much higher conversions obtained in the presence of a small quantity of water compared to those seen in **Table 3.4**. Curiously, the effect was also observed in the case of acetonitrile when the batch reactions are compared, with a 30% increase in conversion following addition of water to the solvent.

Table 3.9 ***Examining the effect of 5% water on the diazo transfer reaction in batch with 5 mol% base***



9 **11**

Entry	***Solvent***	***Ratio***	***Base Loading***	***Reaction Time (min)***	***% Conversion[1]***	***Table 3.4 % Conversion***
1	Acetone : H_2O	95:5	5 mol%	30	45	22
2	EtOH : H_2O	95:5	5 mol%	30	73	56
3	Acetonitrile : H_2O	95:5	5 mol%	30	63	33

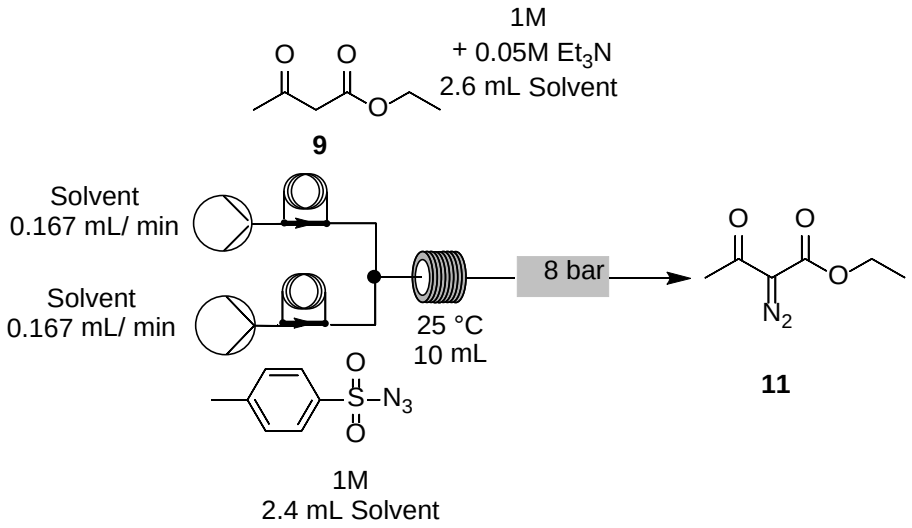
[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

A number of solubility tests were carried out at this point to determine what quantity of water could be added to the solvent mix before *p*-toluenesulfonyl azide **1** becomes immiscible. It

was determined that up to 10% of the solution could be composed of water, but any more than this and solubility issues were encountered.

With this in mind, solutions of 90:10 acetone-water and 90:10 ethanol-water were prepared and used in batch and flow reactions in the presence of 5 mol% triethylamine. **Table 3.10** below outlines the results obtained when 10% water is added to the solvent mixture for diazo transfer in flow.

Table 3.10 ***Examining the effect of 10% water on the diazo transfer reaction in flow***



Entry	*Solvent*	*Ratio*	*Base Loading*	*Reaction Time (min)*	*% Conversion*[1]	*Table 3.6 % Conversions*
1	Acetone : H_2O	90:10	5 mol%	30	97%	57%
2	Acetone : H_2O	90:10	25 mol%	30	100%	-
3	EtOH : H_2O	90:10	5 mol%	30	89%	67%
4	EtOH : H_2O	90:10	5 mol%	60[2]	81%	-

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

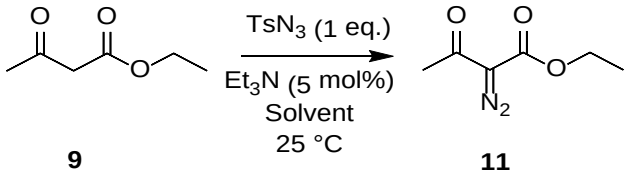
[2] A flow rate of 0.08 mL/min was used for this reaction.

Entries 1 and 3 were carried out initially, and a further increase in conversion was observed with additional water present. In ethanol, 41% conversion was increased to 67% with the addition of 5% water, which was further improved to 89% formation of **11** in the presence of 10% water. For acetone, reactivity improved from 30% with no water present in the solvent, to 57% in the presence of 5% water, until a maximum of 97% conversion to **11** was achieved with 5 mol% triethylamine in 90:10 acetone-water, which is a significant enhancement.

Two other reaction parameters were also explored to see if they had any effect on reaction completion. Firstly, a longer residence time of 60 minutes was carried out, as illustrated in **Table 3.10**, Entry 4. This can be done in one of two ways: two successive tubular reactors may be connected to increase the reactor volume while keeping the flow rate the same, or the existing 10 mL tubular reactor can be used with a lower flow rate. The second approach was taken, using a flow rate of 0.08 mL/min. Disappointingly, this had no positive effect on the efficacy of the reaction and the conversion was actually lower than that observed with a shorter residence time. Increasing the base loading from 5 to 25 mol% (**Table 3.10**, Entry 2) was also attempted in an effort to effect reaction completion. Gratifyingly, the ^{1}H NMR spectrum of the collected product showed 100% conversion to **11** was achieved.

Following on from this success batch reactions were carried out to mirror those done in flow, as outlined in **Table 3.11**. An excellent conversion of 93% was achieved using 5 mol% of triethylamine in 90:10 acetone-water (Entry 1). Interestingly there was no increase in conversion when the base loading was increased fivefold (**Table 3.11**, Entry 2). It is also noteworthy that Entries 3 and 4 below show the same effect as that seen in **Table 3.10** above, whereby the effect of increasing the reaction time from 30 to 60 minutes resulted in a dropoff in conversion. In all cases, conversions were significantly improved when compared to those obtained in **Table 3.7** by addition of an extra 5% water to the solvent mixture.

Table 3.11 ***Examining the effect of 10% water on the diazo transfer reaction in batch***



9 **11**

Entry	*Solvent*	*Ratio*	*Base Loading*	*Reaction Time (min)*	*% Conversion*[1]	*Table 3.7 % Conversions*
1	Acetone : H_2O	90:10	5 mol%	30	93%	45
2	Acetone : H_2O	90:10	25 mol%	30	93%	-
3	EtOH:H_2O	90:10	5 mol%	30	87%	73
4	EtOH:H_2O	90:10	5 mol%	60	84%	-

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^{1}H NMR spectrum of the crude reaction mixture.

3.6 Use of optimised conditions on expanded substrate scope

Although we were very pleased with the results obtained for the flow process, batch experiments which were carried out for validation purposes yielded some excellent results in their own right. Use of 95:5 acetone-water with one equivalent of base resulted in 92% conversion to the desired product in only 30 minutes (**Table 3.7**, Entry 1).When the base loading was then reduced to 5 mol% and used in conjunction with 90:10 acetone-water, an improved conversion of 93% was obtained. 90:10 ethanol-water was also a very effective solvent when used with 5 mol% triethylamine, resulting in 87% conversion. These results are very promising and represent the highest conversions for these short reaction times in batch observed to date.

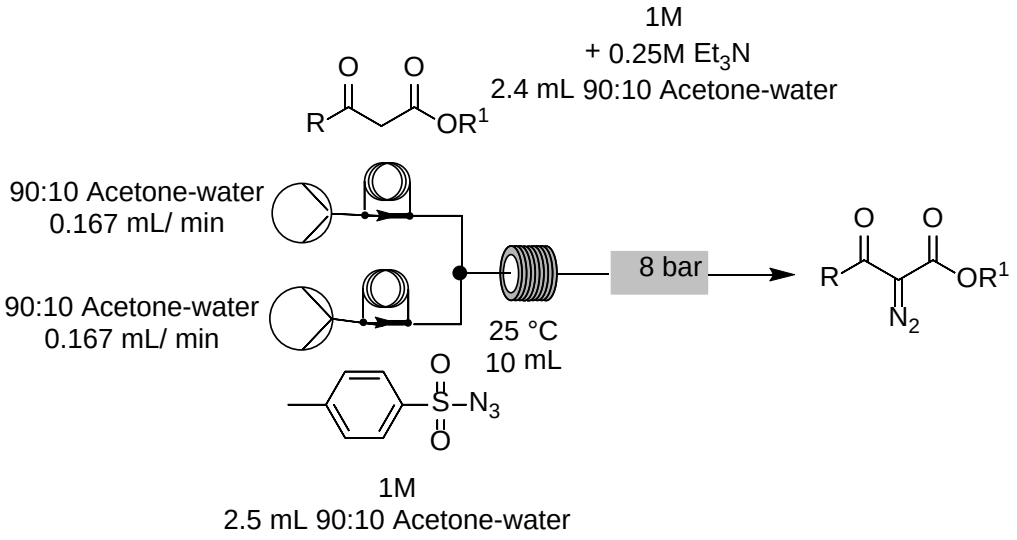
Several promising results were obtained in the course of investigating the optimum conditions for diazo transfer in flow. When one equivalent of base was employed with either

90:10 acetone-water or 90:10 acetonitrile-water, 98% conversion was obtained (**Table 3.6**, Entries 1 and 4). When the base loading was reduced to 5 mol% with the same solvents, outstanding conversions of 97 and 89% were obtained respectively (**Table 3.10**, Entries 1 and 3).

However, two sets of conditions were identified as giving the best conversions in flow. The use of either 95:5 ethyl acetate-water or 95:5 ethanol-water in conjunction with one equivalent of triethylamine furnished 100% conversion (**Table 3.6**). The same conversion was achieved using 90:10 acetone-water and 25 mol% triethylamine.

When considering which solvent to use as the primary component of the solvent for the reaction, the reports by GlaxoSmithKline and the American Chemical Society Green Chemistry Institute which had been used to choose the solvents initially were consulted again, and acetone was determined to be the best of the three solvents.[41,42] In addition to this, acetone allowed a reduction in the base loading to 25 mol%. Although this loading is not a true catalytic loading, it is still a 75% reduction in the quantity of base required. Therefore, the use of 25 mol% of triethylamine in 90:10 acetone-water were identified as the optimum conditions for these reactions, and were subsequently applied to a range of β-ketoesters, as illustrated in **Table 3.12**.

Table 3.12 ***Use of optimised conditions on expanded substrate scope in flow***



Entry	*R*	*R¹*	*Diazo Product*	*% Conversion[1]*
1	Me	*t*-Butyl	**12**	94
2	Me	Pentyl	**13**	100
3	Me	2-Ethylbutyl	**16**	95
4	Me	3,7-dimethyloct-6-enyl	**18**	100
5	Me	Undec-10-en-1-yl	**17**	100
6	*n*-Propyl	Et	**15**	96

[1] % Conversion calculated from appropriate peak with key signal change in the ^{1}H NMR spectrum between starting material and product.

We are pleased to report excellent conversions were achieved in all cases. It is interesting to note that the β-ketoesters with the longest ester side chains gave the best conversions, with complete consumption of the starting material. The ^{1}H NMR spectra of these reaction mixtures were clean of any impurities except for *p*-toluenesulfonyl azide **1** and *p*-toluenesulfonyl amide **2** as expected. This is illustrated in **Figure 3.2** below, which shows the ^{1}H NMR spectrum of the crude reaction mixture from Entry 5 in **Table 3.12** above.

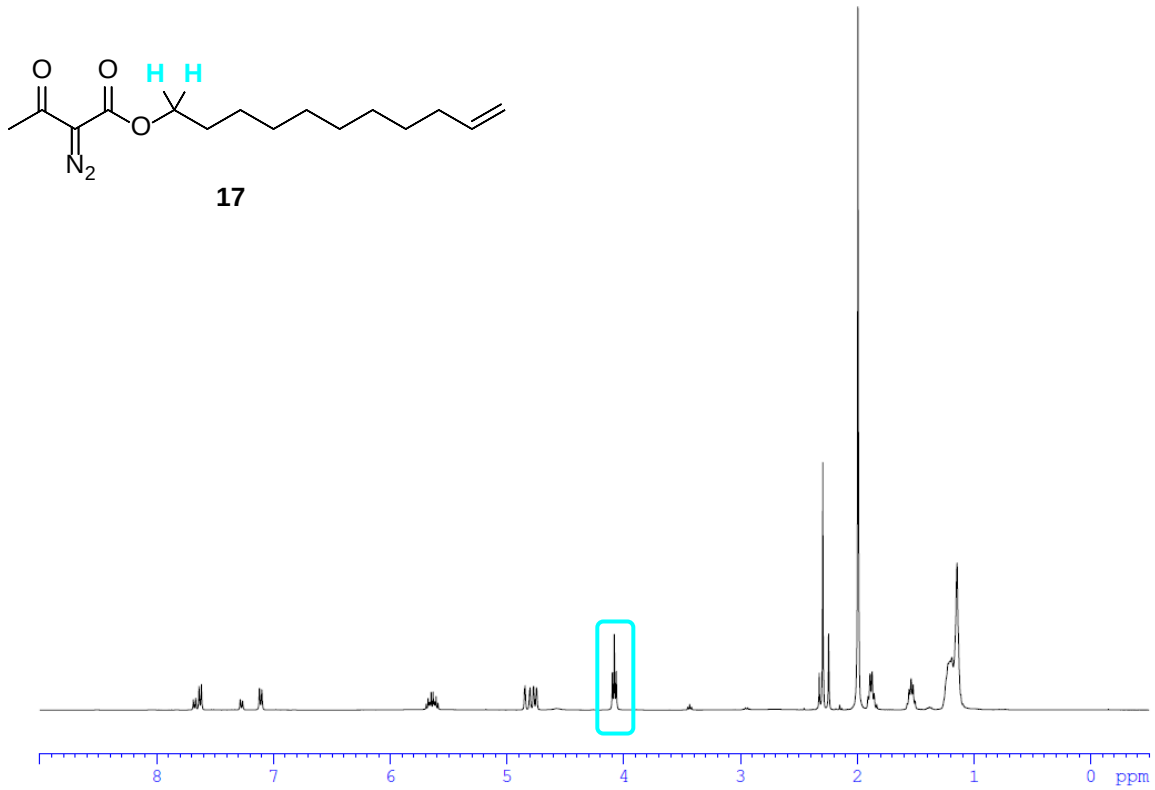
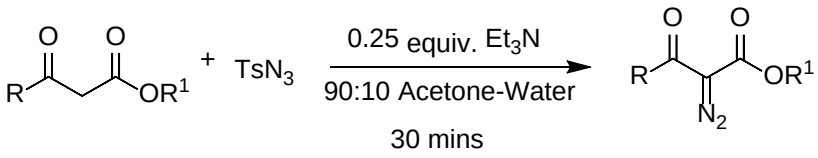


Figure 3.2 ^{1}H NMR spectrum of crude reaction mixture of Entry 5, Table **3.12**.

Table 3.13 ***Use of optimised conditions on expanded substrate scope in batch***



Entry	*R*	*R^{1}*	*Diazo Product*	*% Conversion^{1}*
1	Me	*t*-Butyl	**12**	96
2	Me	Pentyl	**13**	88
3	Me	2-Ethylbutyl	**16**	92
4	Me	3,7-dimethyloct-6-enyl	**18**	98
5	Me	Undec-10-en-1-yl	**17**	93
6	*n*-Propyl	Et	**15**	86

[1] % Conversion calculated from appropriate peak with key signal change in the ^{1}H NMR spectrum between starting material and product.

When the same reaction conditions were employed in batch, good to excellent conversions were also achieved. Though not as efficient as in flow, it should be noted that these high conversions in such a short reaction time in batch is unprecedented in our research. Overall, we were delighted with the efficacy of these reactions, carried out under green conditions.

Subsequent to this research, other work within the group developed a method to prepare *p*-toluenesulfonyl azide **1** *in situ* and subsequently carry out diazo transfer to a range of substrates in a telescoped reaction.[44] Future work in this area will include the coupling of both projects to develop a method for preparation of **1** *in situ*, and subsequent diazo transfer using the green optimised conditions above.

3.7 Use of immobilised diazo transfer reagent in flow

The role of solid-supported reagents for synthesis in continuous processing has been reviewed in the literature.[45,46] Whether these solid-supported reagents are used as scavengers to remove by-products from the reaction stream, or as active reagents in the reaction, they are used by directing a continuous stream through a cartridge or column which is packed with the solid in question. In the case where the solid-supported reagent is playing an active role in the reaction, this column or cartridge assumes the role of the tubular reactor in liquid only reactions. Therefore the reactor volume is determined by calculating the empty volume between the beads of the polymer in the column or cartridge.

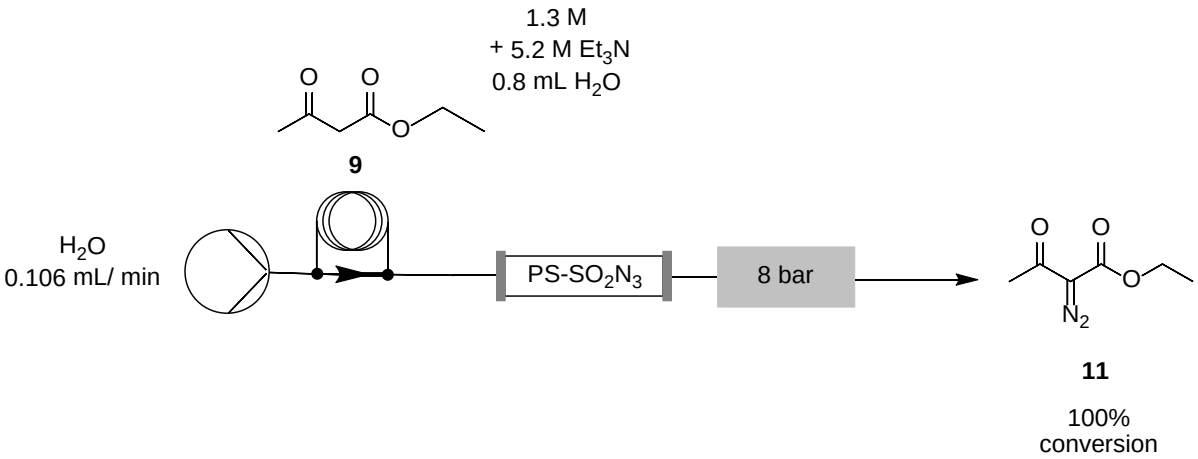
The use of polymer-supported benzenesulfonyl azide **25** is cost prohibitive in continuous processing due to the large quantities required to pack the column or cartridge as described above. **Section 2.5** outlined the synthesis of polymer-supported benzenesulfonyl azide **25** *via* an independently synthesised benzenesulfonyl chloride **26** resulting in a significantly reduced cost per gram for this reagent – approximately €0.35 per gram of **26** versus €15 per gram of **26** when purchased commercially.

Although initial experiments were carried out using 3 equivalents of **25** in the column reactor, this resulted in low conversions for the reaction. After various attempts to use sand as a filler to increase the residence time, it was decided to fill the Omnifit column to capacity with

polymer-supported benzenesulfonyl azide **25** (approximately 3.7 g, 16.6 mmol, ~4 equivalents), which could then be re-used.

The set-up for use of polymer-supported benzenesulfonyl azide required use of one pump only. The mixture of β-ketoester and base in solvent was prepared and injected using sample loops. It was possible to use water as the solvent for these reactions, as there is no longer solubility issues with *p*-toluenesulfonyl azide **1**. A continuous stream of the reagents in water was pumped through an Omnifit glass column packed with pre-prepared polymer-supported benzenesulfonyl azide **25** as illustrated in **Scheme 3.8**. When using solid-supported reagents in this manner it is important to regulate the pressure by use of a back pressure regulator (BPR).

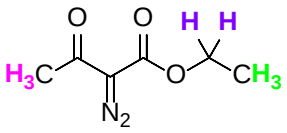
Initial experiments were carried out at 1M concentrations, however a slight increase to 1.3M solutions of ethyl acetoacetate **9** resulted in an improvement in conversion during the early optimisation of these reactions.



Scheme 3.8

Green and co-workers reported the use of polymer-supported benzenesulfonyl azide **25** with a threefold excess of base in their original paper.[39] Therefore our initial experiment was carried out using three equivalents of base. Following extraction of the collected sample into ethyl acetate, the ^{1}H NMR spectrum of the crude reaction mixture showed 100% conversion to ethyl 2-diazo-3-oxobutanoate **11**, as shown in **Figure 3.3** below. As can be seen, the samples obtained from this reaction is pure diazo product **11**. This is due to the use of

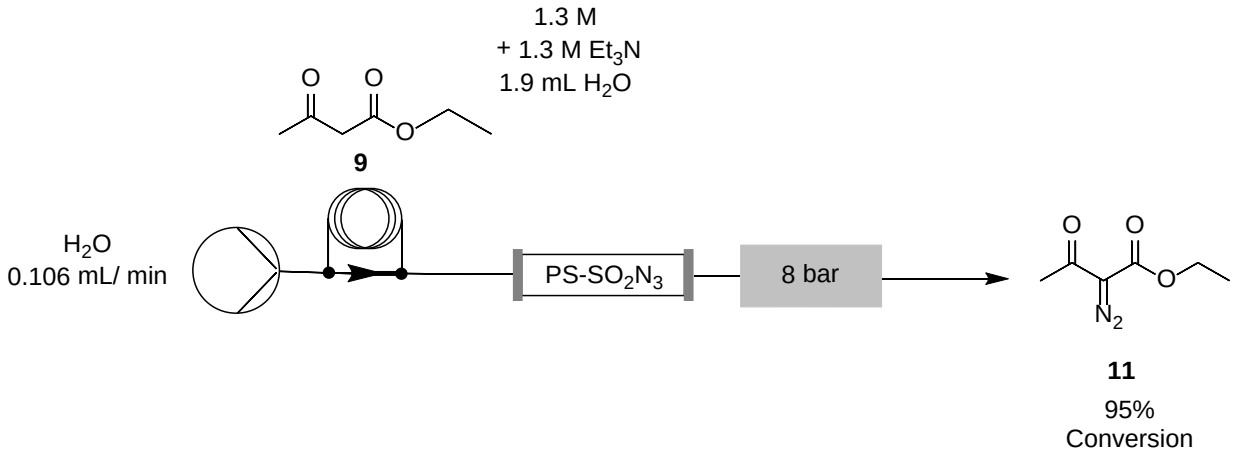
polymer-supported benzenesulfonyl azide **25**, as both the azide and the amide side product remain adsorbed on the polymer, resulting in pure products without the need for chromatography.



11

Figure 3.3 ^{1}H NMR spectrum of the crude reaction mixture from the flow reaction outlined above in **Scheme 3.8**.

Encouraged by this very positive result, it was decided to attempt the same reaction using a stoichiometric quantity of base, as shown in **Scheme 3.9**.



Scheme 3.9

Following extraction of the crude reaction mixture into ethyl acetate, a ^{1}H NMR spectrum of the crude reaction mixture was obtained which showed 95% conversion to the desired product. We were delighted with this result, which showed efficient diazo transfer to ethyl acetoacetate **9** in a flow reactor using water as a solvent and an in-house prepared polymer-supported benzenesulfonyl azide as the diazo transfer reagent.

3.8 Conclusions

Several screens were carried out to determine the optimum reaction conditions for a green approach to diazo transfer in a flow reactor. Due to solubility issues associated with *p*-toluenesulfonyl azide **1** in water, it was determined to be an unsuitable solvent for use by itself in this flow process. After consulting the literature acetone, ethyl acetate and ethanol were chosen as alternative green solvents.

Following the discovery that a small quantity of water in the reaction solvent promotes efficient diazo transfer, several excellent results were obtained for diazo transfer in flow. As described above, these included use of 5 mol% base in acetone or ethanol in the presence of 10% water. The optimum conditions were determined to be use of 25 mol% triethylamine in 90:10 acetone-water. These conditions were successfully employed to synthesise a range of α-diazo-β-ketoesters.

Significant results were also obtained for diazo transfer in batch using green reaction conditions. Up to 93% conversion was achieved in 30 minutes when 5 mol% triethylamine was used in conjunction with 90:10 acetone-water.

In addition to this, the polymer-supported benzenesulfonyl azide **25** previously synthesised in **Section 2.5** was used to carry out efficient diazo transfer to ethyl acetoacetate **9**. This was achieved at base loading of three and one equivalents, using water as a reaction solvent to give conversions of 100 and 95% respectively. Future work on this project will include investigation into carrying out diazo transfer in flow, using 0.25 equivalents of triethylamine in conjunction with the polymer-supported benzenesulfonyl azide.

3.9 References

[1] B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chemie, Int. Ed.* **2015**, *54*, 6688–6728.

[2] B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. - A Eur. J.* **2015**, *21*, 2298–2308.

[3] S. T. R. Mueller, T. Wirth, *ChemSusChem* **2015**, *8*, 245–250.

[4] I. R. Baxendale, L. Brocken, C. J. Mallia, *Green Process. Synth.* **2013**, *2*, 211–230.

[5] T. N. Glasnov, C. O. Kappe, *Chem. - A Eur. J.* **2011**, *17*, 11956–11968.

[6] R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chemie, Int. Ed.* **2011**, *50*, 7502–7519.

[7] D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389.

[8] J. C. Pastre, D. L. Browne, S. V Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849–8869.

[9] D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680.

[10] J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57.

[11] S. V Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chemie, Int. Ed.* **2015**, *54*, 10122–10136.

[12] J. Sedelmeier, S. V Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618–3621.

[13] O. Shvydkiv, A. Yavorskyy, K. Nolan, M. Oelgemoller, *EPA Newsl.* **2012**, 65–69.

[14] A. Yavorskyy, O. Shvydkiv, K. Nolan, N. Hoffmann, M. Oelgemoller, *Tetrahedron Lett.* **2011**, *52*, 278–280.

[15] A. Yavorskyy, O. Shvydkiv, N. Hoffmann, K. Nolan, M. Oelgemoller, *Org. Lett.* **2012**, *14*, 4342–4345.

[16] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *Tetrahedron* **2013**, *69*, 2276–2282.

[17] R. C. R. Wootton, R. Fortt, A. J. de Mello, *Lab Chip* **2002**, *2*, 5–7.

[18] R. Fortt, R. C. R. Wootton, A. J. de Mello, *Org. Process Res. Dev.* **2003**, *7*, 762–768.

[19] B. Ahmed-Omer, D. A. Barrow, T. Wirth, *Tetrahedron Lett.* **2009**, *50*, 3352–3355.

[20] B. Ahmed, D. Barrow, T. Wirth, *Adv. Synth. Catal.* **2006**, *348*, 1043–1048.

[21] Z. Yu, Y. Lv, C. Yu, *Org. Process Res. Dev.* **2012**, *16*, 1669–1672.

[22] Z. Yu, Y. Lv, C. Yu, W. Su, *Tetrahedron Lett.* **2013**, *54*, 1261–1263.

[23] L. Malet-Sanz, J. Madrzak, S. V Ley, I. R. Baxendale, *Org. Biomol. Chem.* **2010**, *8*, 5324–5332.

[24] J. Jacq, P. Pasau, *Chem. - A Eur. J.* **2014**, *20*, 12223–12233.

[25] R. A. Maurya, K.-I. Min, D.-P. Kim, *Green Chem.* **2014**, *16*, 116–120.

[26] S. T. R. Muller, D. Smith, P. Hellier, T. Wirth, *Synlett* **2014**, *25*, 871–875.

[27] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *J. Org. Chem.* **2010**, *75*, 8674–8676.

[28] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *Chem. - A Eur. J.* **2011**, *17*, 9586–9589.

[29] L. J. Martin, A. L. Marzinzik, S. V Ley, I. R. Baxendale, *Org. Lett.* **2011**, *13*, 320–323.

[30] R. C. Wheeler, O. Benali, M. Deal, E. Farrant, S. J. F. MacDonald, B. H. Warrington, *Org. Process Res. Dev.* **2007**, *11*, 704–710.

[31] M. M. E. Delville, P. J. Nieuwland, P. Janssen, K. Koch, J. C. M. van Hest, F. P. J. T. Rutjes, *Chem. Eng. J.* **2011**, *167*, 556–559.

[32] S. T. R. Mueller, A. Murat, D. Maillos, P. Lesimple, P. Hellier, T. Wirth, *Chem. - A Eur. J.* **2015**, *21*, 7016–7020.

[33] S. T. R. Muller, A. Murat, P. Hellier, T. Wirth, *Org. Process Res. Dev.* **2016**, *20*, 495-502.

[34] L. D. Tuma, *Thermochim. Acta* **1994**, *243*, 161–167.

[35] F. W. Bollinger, L. D. Tuma, *Synlett* **1996**, 407–413.

[36] A. R. Katritzky, M. El Khatib, O. Bol'shakov, L. Khelashvili, P. J. Steel, *J. Org. Chem.* **2010**, *75*, 6532-6539.

[37] M. K. Muthyala, S. Choudhary, A. Kumar, *J. Org. Chem.* **2012**, *77*, 8787–8791.

[38] A. M. Harned, W. M. Sherrill, D. L. Flynn, P. R. Hanson, *Tetrahedron* **2005**, *61*, 12093–12099.

[39] G. M. Green, N. P. Peet, W. A. Metz, *J. Org. Chem.* **2001**, *66*, 2509–2511.

[40] E. D. Goddard-Borger, R. V Stick, *Org. Lett.* **2007**, *9*, 3797–3800.

[41] A. G. C. Institute, *ACS GCI Pharmaceutical Roundtable Solvent Selection Guide*, **2011**.

[42] R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854–862.

[43] E. Tarrant, New Insights into the Synthesis of α-Diazocarbonyl Compounds and Their Decomposition Pathways, PhD Thesis, University College Cork, **2012**.

[44] B. J. Deadman, R. M. O'Mahony, D. Lynch, D. C. Crowley, S. G. Collins, A. R. Maguire, *Org. Biomol. Chem.* **2016**, *14*, 3423-3431.

[45] I. R. Baxendale, S. V Ley, *Ernst Schering Found. Symp. Proc.* **2006**, 151–185.

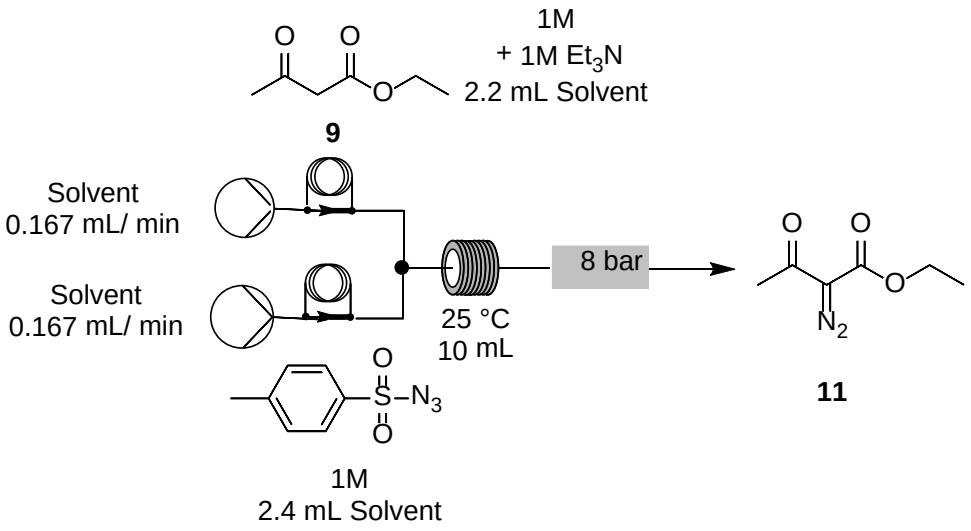
[46] S. V Ley, I. R. Baxendale, R. M. Myers, in Combinatorial Synthesis of Natural Product-Based Libraries, CRC Press LLC, **2006**, pp. 131–163.

Chapter 3

Experimental

Table of Contents

3.1 Initial investigation into diazo transfer using flow reactor



Representative Procedure

A solution of ethyl acetoacetate **9** (0.39 g, 3 mmol) and triethylamine (0.42 mL, 3 mmol) in acetone (2.2 mL) (0.167 mL/min) and a solution of *p*-toluenesulfonyl azide **1** (0.59 g, 3 mmol) in acetone (2.4 mL) (0.167 mL/ min) were injected through 2 mL injection loops using 5 mL plastic syringes and combined at a T-piece. The reagents were then reacted in a 10 mL PFA reactor at 25 °C (30 min residence time). The reactor was maintained at 8 bar back pressure by a back pressure regulator (BPR). A dispersion curve is generated by Flow Commander software, which mathematically predicts when the maximum of product will elute from the reactor, thereby determining the collection point. There should be no product eluted on either side of this curve. The collected solution obtained was concentrated *in vacuo*. Results are summarised below. Spectral details as listed previously.

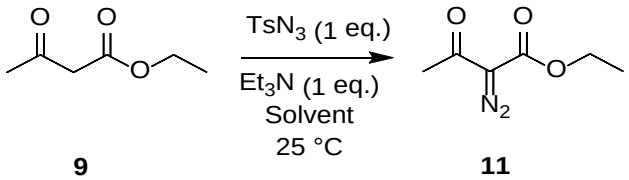
Entry	***Solvent***	***Residence Time (min)***	***Temperature (°C)***	***% Conversion[1]***
1	Acetone	30	25	76
2	Ethyl Acetate	30	25	66
3	Ethanol	30	25	96
4	Acetonitrile	30	25	68

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

Comparison reactions in batch – 30 mins

Representative Procedure

A solution of *p* –toluenesulfonyl azide **1** (0.39 g, 2 mmol) in acetone (1.7 mL) was added dropwise to a stirring solution of ethyl acetoacetate **9** (0.26 g, 2 mmol) and triethylamine (0.28 mL, 2 mmol) in acetone (1.5 mL). The reaction was stirred at room temperature for 30 min, then the solvent was removed *in vacuo*. Results are summarised below. Spectral details as listed previously.

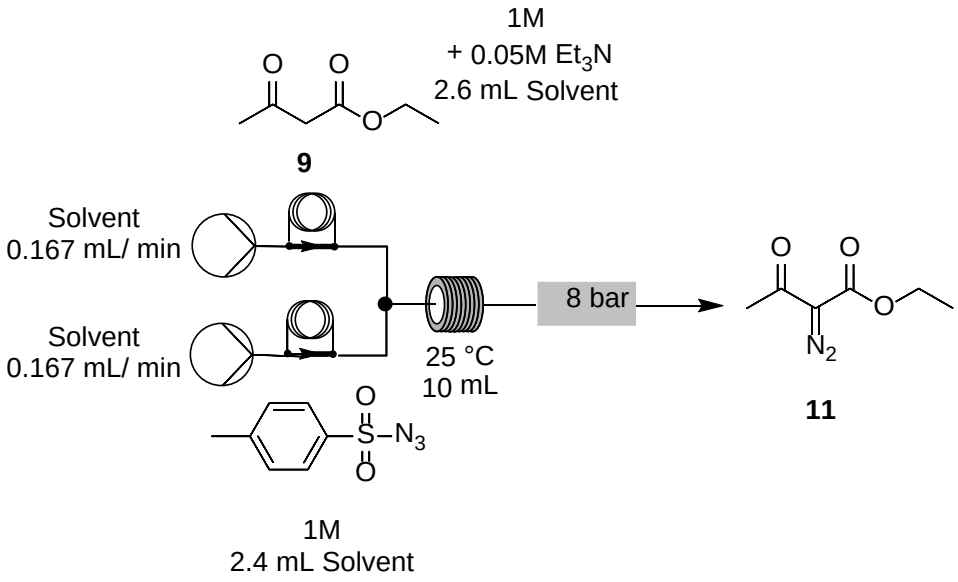


9 **11**

Entry	***Solvent***	***Reaction Time (min)***	***Temperature (°C)***	***% Conversion[1]***
1	Acetone	30	25	85
2	Ethyl Acetate	30	25	62
3	Ethanol	30	25	91
4	Acetonitrile	30	25	93

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

3.2 Initial Investigation into diazo transfer using flow reactor using catalytic amount of base



Representative Procedure

A solution of ethyl acetoacetate **9** (0.39 g, 3 mmol) and triethylamine (21 µL, 0.15 mmol) in acetone (2.6 mL) (0.167 mL/min) and a solution of *p*-toluenesulfonyl azide **1** (0.59 g, 3 mmol) in acetone (2.4 mL) were injected through 2 mL injection loops, combined at a T-piece and then reacted in a 10 mL PFA reactor at 25 °C (30 min residence time). The reactor was maintained at 8 bar back pressure by a BPR. The solution obtained was concentrated *in vacuo*. Results are summarised below. Spectral details as listed previously.

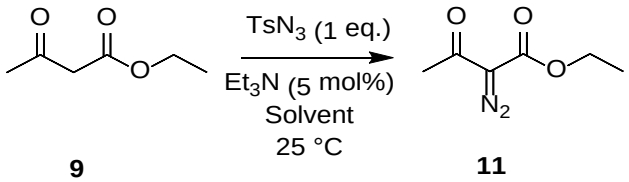
Entry	***Solvent***	***Base Loading***	***Residence Time (min)***	***Temperature (°C)***	***% Conversion[1]***
1	Acetone	5 mol%	30	25	30
2	Ethanol	5 mol%	30	25	41
3	Acetonitrile	5 mol%	30	25	39
4	Ethanol	25 mol%	30	25	95

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

Comparison reactions in batch – 30 mins

Representative Procedure

A solution of *p*-toluenesulfonyl azide **1** (0.39 g, 2 mmol) in acetone (1.7 mL) was added dropwise to a stirring solution of ethyl acetoacetate **9** (0.26 g, 2 mmol) and triethylamine (14 µL, 0.15 mmol) in acetone (1.7 mL). The reaction was stirred at room temperature for 30 min, then the solvent was removed *in vacuo*. Results are summarised below. Spectral details as listed previously.

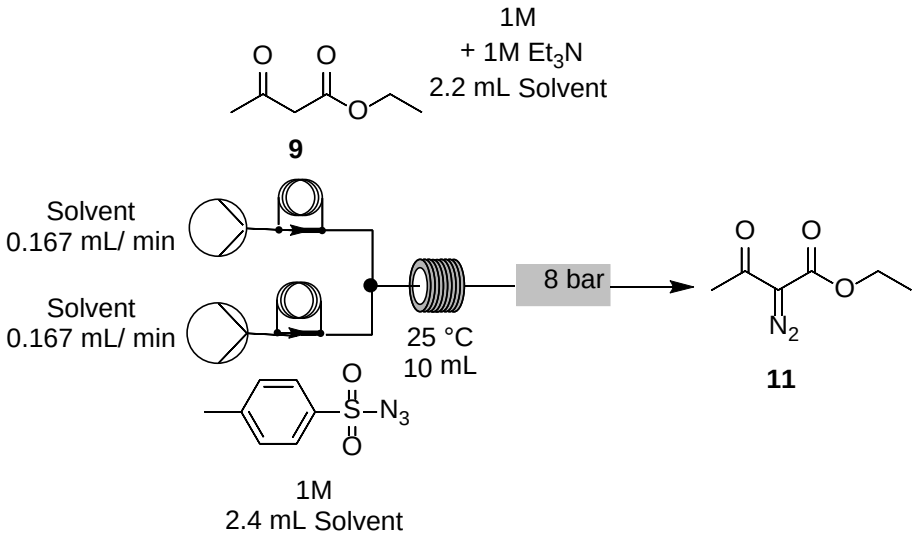


9 **11**

Entry	***Solvent***	***Base Loading***	***Reaction Time (min)***	***Temperature (°C)***	***% Conversion[1]***
1	Acetone	5 mol%	30	25	22
2	Ethanol	5 mol%	30	25	56
3	Acetonitrile	5 mol%	30	25	33
4	Ethanol	25 mol%	30	25	84

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

3.3 Investigating effect of water on reaction efficiency



Representative Procedure

A solution of ethyl acetoacetate **9** (0.39 g, 3 mmol) and triethylamine (0.42 mL, 3 mmol) in acetone-water (95:5) (2.2 mL) (0.167 mL/min) and a solution of *p*-toluenesulfonyl azide **1** (0.59 g, 3 mmol) in acetone-water (95:5) (2.4 mL) (0.167 mL/ min) were injected through 2 mL injection loops using 5 mL plastic syringes and combined at a T-piece. The reagents were then reacted in a 10 mL PFA reactor at 25 °C (30 min residence time). The reactor was maintained at 8 bar back pressure by a back pressure regulator (BPR). Flow Commander software was used to determine the collection point. The collected solution obtained was concentrated *in vacuo*. Results are summarised below. Spectral details as listed previously.

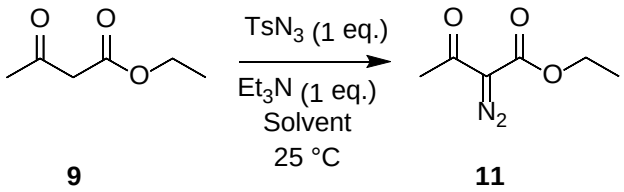
Entry	***Solvent***	***Ratio***	***Residence Time (min)***	***Temperature (°C)***	***% Conversion***
1	Acetone:H_2O	95:5	30	25	98
2	Ethyl Acetate:H_2O	95:5	30	25	100
3	Ethanol:H_2O	95:5	30	25	100
4	Acetonitrile:H_2O	95:5	30	25	98

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

Comparison reactions in batch – 30 mins

Representative Procedure

A solution of *p* –toluenesulfonyl azide **1** (0.39 g, 2 mmol) in acetone – water (95:5) (1.7 mL) was added dropwise to a stirring solution of ethyl acetoacetate **9** (0.26 g, 2 mmol) and triethylamine (0.28 mL, 2 mmol) in acetone – water (95:5) (1.5 mL). The reaction was stirred at room temperature for 30 min, then the solvent was removed *in vacuo*. Results are summarised below. Spectral details as listed previously.

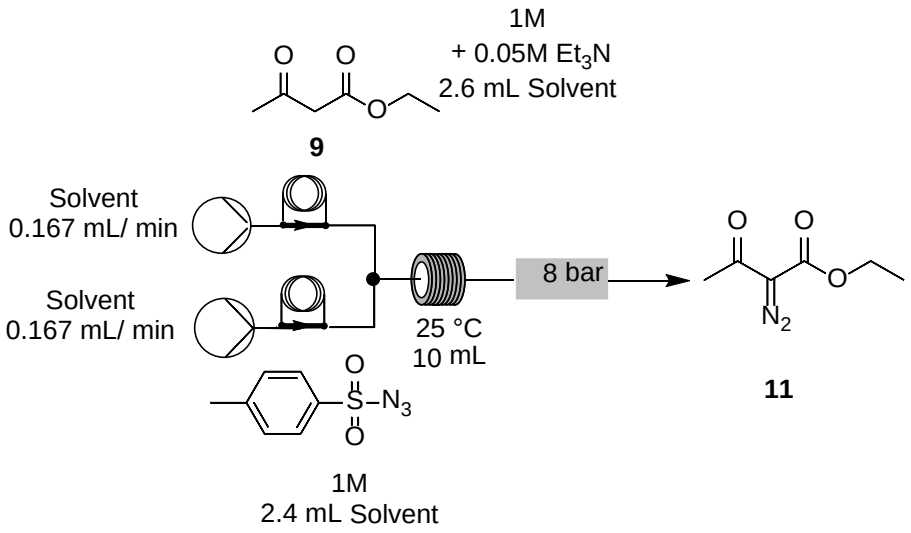


9 **11**

Entry	***Solvent***	***Ratio***	***Reaction Time (min)***	***Temperature (°C)***	***% Conversion[1]***
1	Acetone:H_2O	95:5	30	25	92
2	Ethyl Acetate:H_2O	95:5	30	25	84
3	Ethanol:H_2O	95:5	30	25	89
4	Acetonitrile:H_2O	95:5	30	25	93

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

3.4 Investigating effect of water on reaction efficiency – catalytic quantity of base



Representative Procedure

A solution of ethyl acetoacetate **9** (0.39 g, 3 mmol) and triethylamine (21 µL, 0.15 mmol) in ethanol-water (95:5) (2.6 mL) (0.167 mL/min) and a solution of *p*-toluenesulfonyl azide **1** (0.59 g, 3 mmol) in in ethanol-water (95:5) (2.4 mL) were injected through 2 mL injection loops using 5 mL plastic syringes and combined at a T-piece. The reagents were then reacted in a 10 mL PFA reactor at 25 °C (30 min residence time). The reactor was maintained at 8 bar back pressure by a back pressure regulator (BPR). Flow Commander software was used to determine the collection point. The collected solution obtained was concentrated *in vacuo*. Results are summarised below. Spectral details as listed previously.

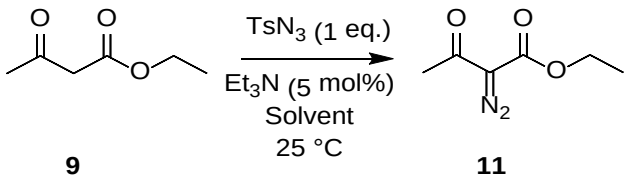
Entry	***Solvent***	***Ratio***	***Base Loading***	***Reaction Time (min)***	***Temperature (°C)***	***% Conversion[1]***
1	EtOH : H_2O	95:5	5 mol%	30	25	67
2	Acetone : H_2O	95:5	5 mol%	30	25	57
3	Acetonitrile : H_2O	95:5	5 mol%	30	25	46
4	EtOH : H_2O	90:10	5 mol%	30	25	89
5	EtOH : H_2O	90:10	5 mol%	60	25	81
6	Acetone : H_2O	90:10	5 mol%	30	25	97
7	Acetone : H_2O	90:10	25 mol%	30	25	100

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

Comparison reactions in batch – 30 mins

Representative Procedure

A solution of *p* –toluenesulfonyl azide **1** (0.39 g, 2 mmol) in ethanol-water (95:5) (1.7 mL) was added dropwise to a stirring solution of ethyl acetoacetate **9** (0.26 g, 2 mmol) and triethylamine (14 µL, 0.1 mmol) in ethanol-water (95:5) (1.7 mL). The reaction was stirred at room temperature for 30 min, then the solvent was removed *in vacuo*. Results are summarised below. Spectral details as listed previously.

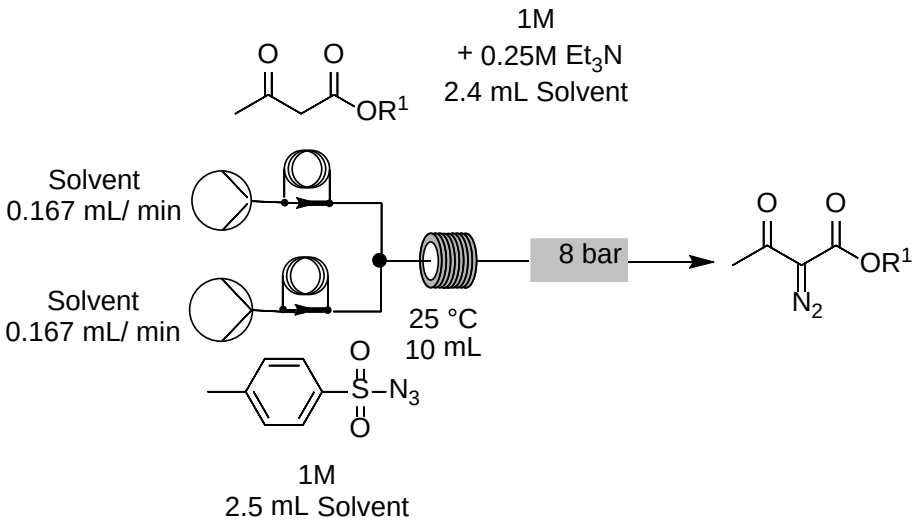


9 **11**

Entry	***Solvent***	***Ratio***	***Base Loading***	***Reaction Time (min)***	***Temperature (°C)***	***% Conversion[1]***
1	EtOH : H_2O	95:5	5 mol%	30	25	73
2	Acetone : H_2O	95:5	5 mol%	30	25	45
3	Acetonitrile : H_2O	95:5	5 mol%	30	25	63
4	EtOH:H_2O	90:10	5 mol%	30	25	87
5	EtOH:H_2O	90:10	5 mol%	60	25	84
6	Acetone : H_2O	90:10	5 mol%	30	25	93
7	Acetone : H_2O	90:10	25 mol%	30	25	93

[1] Conversions calculated from ratio of starting material to product using CH_2 quartet of ester side chain in the ^1H NMR spectrum of the crude reaction mixture.

3.5 Use of optimised conditions on expanded substrate scope



Representative Procedure

A solution of *t*-butyl acetoacetate **23** (0.48 g, 3 mmol) and triethylamine (0.11 mL, 0.75 mmol, 0.25 eq.) in acetone-water (90:10) (2.4 mL) (0.167 mL/min) and a solution of *p*-toluenesulfonyl azide **1** (0.59 g, 3 mmol) in acetone-water (90:10) (2.5 mL) (0.167 mL/ min) were injected through 2 mL injection loops using 5 mL plastic syringes and combined at a T-piece. The reagents were then reacted in a 10 mL PFA reactor at 25 °C (30 min residence time). The reactor was maintained at 8 bar back pressure by a back pressure regulator (BPR). Flow Commander software was used to determine the collection point. The collected solution obtained was concentrated *in vacuo*. Results are summarised below. Spectral details as listed previously.

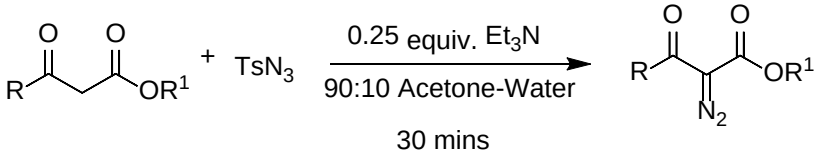
Entry	***R***	***R[1]***	***Diazo Product***	***% Conversion[1]***
1	Me	*t*-Butyl	**12**	94
2	Me	Pentyl	**13**	100
3	Me	2-Ethylbutyl	**16**	95
4	Me	3,7-dimethyloct-6-enyl	**18**	100
5	Me	Undec-10-en-1-yl	**17**	100
6	*n*-Propyl	Et	**15**	96

[1] % Conversion calculated from appropriate peak with key signal change in the ^{1}H NMR spectrum between starting material and product.

Comparison reactions in batch – 30 mins

Representative Procedure

A solution of *p* –toluenesulfonyl azide **1** (0.39 g, 2 mmol) in acetone – water (90:10) (1.7 mL) was added dropwise to a stirring solution of *t*-butyl acetoacetate **23** (0.32 g, 2 mmol) and triethylamine (0.07 mL, 0.5 mmol, 0.25 eq.) in acetone – water (90:10) (1.6 mL). The reaction was stirred at room temperature for 30 min, then the solvent was removed *in vacuo*. Results are summarised below. Spectral details as listed previously.

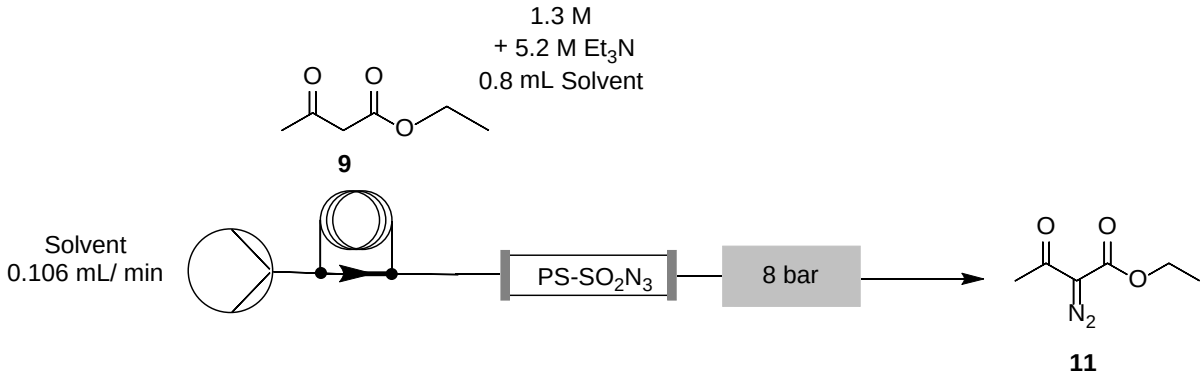


Entry	***R***	***R[1]***	***Diazo Product***	***% Conversion[1]***
1	Me	*t*-Butyl	**12**	96
2	Me	Pentyl	**13**	88
3	Me	2-Ethylbutyl	**16**	92
4	Me	3,7-dimethyloct-6-enyl	**18**	98
5	Me	Undec-10-en-1-yl	**17**	93
6	*n*-Propyl	Et	**15**	86

[1] % Conversion calculated from appropriate peak with key signal change in the ^{1}H NMR spectrum between starting material and product.

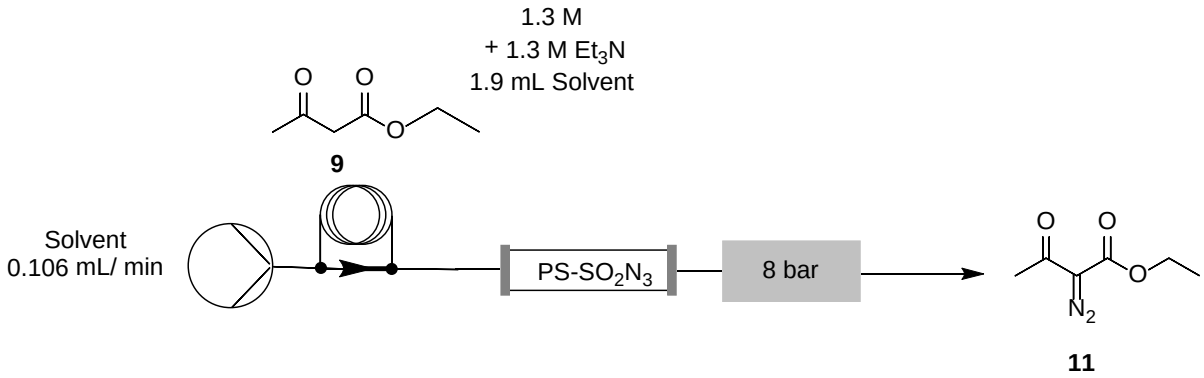
3.6 Use of immobilised diazo transfer reagent in flow

3.6.1 Immobilised diazo transfer reagent with 3eq. base



A solution of ethyl acetoacetate **9** (0.52 g, 4 mmol) and triethylamine (1.67 mL, 12 mmol, 3 eq.) in water (0.82 mL) (0.106 mL/min) was injected through a 2 mL injection loop using a 5 mL plastic syringe. This solution was then flowed through an Omnifit glass column which was pre-packed with polymer-supported benzenesulfonyl azide **25** previously synthesised in **Section 2.5.2**. The reactor volume was determined to be 3.96 mL, therefore a flow rate of 0.106 mL/min gave a residence time of 37.5 minutes. The reactor was maintained at 8 bar back pressure by a back pressure regulator (BPR). Flow Commander software was used to determine the collection point. The collected solution obtained was extracted with 3 x 15 mL ethyl acetate, and then dried, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude reaction mixture showed 100% conversion to the desired product. Spectral details as listed previously.

3.6.2 Immobilised diazo transfer reagent with 1eq. base



A 1.3M solution of ethyl acetoacetate **9** (0.52 g, 4 mmol) and triethylamine (0.56 mL, 4 mmol, 1 eq.) in water (0.82 mL) (0.106 mL/min) was injected through a 2 mL injection loop using a 5 mL plastic syringe. This solution was then pumped through an Omnifit glass column which was pre-packed with polymer-supported benzenesulfonyl azide **25** previously synthesised in **Section 2.5.2**. A flow rate of 0.106 mL/min was used, giving a residence time of 37.5 minutes in the 3.96 mL reactor. The reactor was maintained at 8 bar back pressure by a back pressure regulator (BPR). Flow Commander software was used to determine the collection point. The collected solution obtained was extracted with 3 x 15 mL ethyl acetate, and then dried, filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude reaction mixture showed 95% conversion to the desired product. Spectral details as listed previously.

Chapter 4

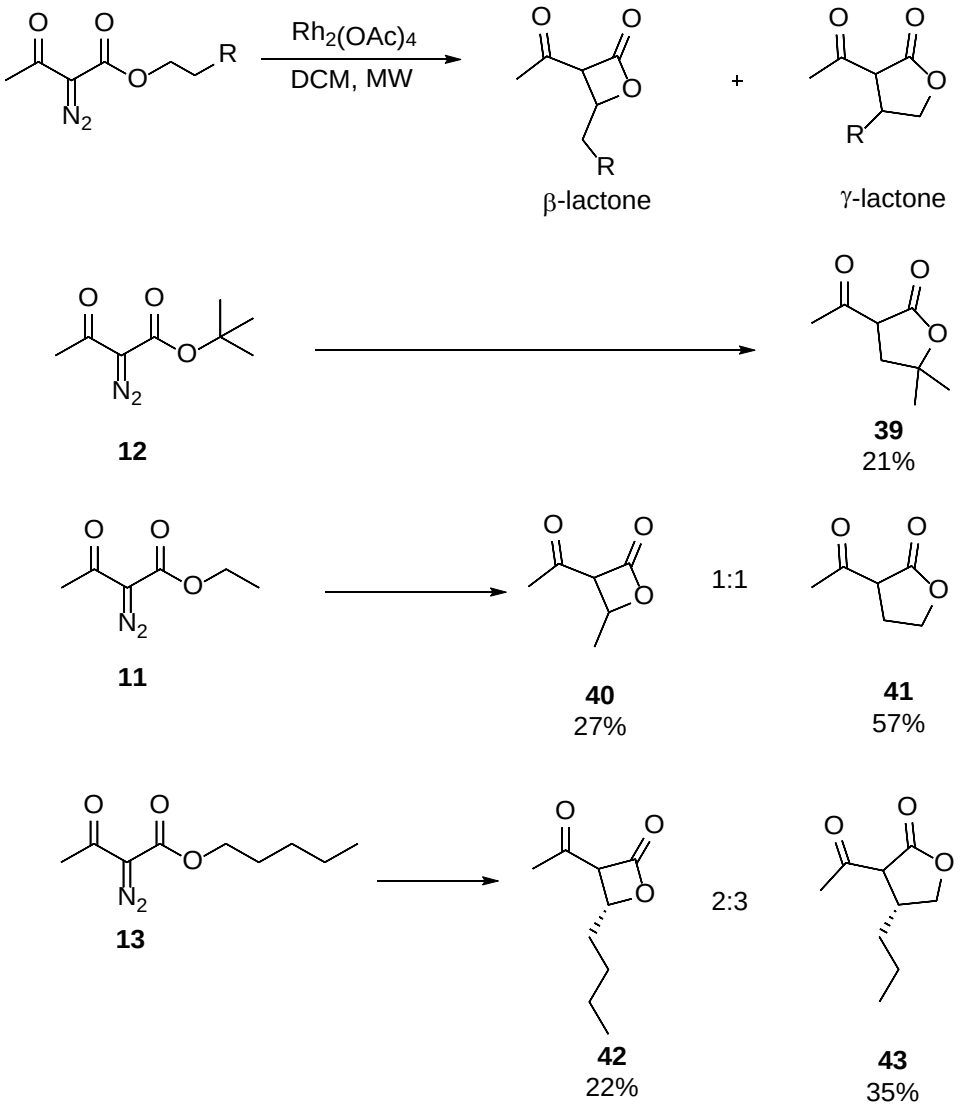
Results and Discussion

Table of Contents

4.1 A novel approach to dioxinone derivatives

4.1.1 Introduction and objectives

α-Diazocarbonyl compounds are extremely useful in organic synthesis due to their ease of preparation and their diverse reactivity. Decomposition of these compounds under thermolysis, photolysis or transition metal catalysis generates a carbenoid intermediate, which can then undergo a range of reaction pathways. Previous work carried out within the group focused on one of these reaction pathways, using rhodium(II) catalysed decomposition of α-diazo-β-ketoesters to synthesise a range of β- and γ-lactones, as shown below in **Scheme 4.1**.[1]



Scheme 4.1

In the course of this previous research, the decomposition of three α-diazo-β-ketoester derivatives **44**-**46** resulted in the formation of unexpected dioxinone products. From examination of the α-diazo-β-ketoesters which gave rise to this type of product, it was proposed that the dioxinone may be formed only in cases where a stabilised carbocation could be formed at the α-position in the ester side-chain, and is stabilised either by inductive (**44** and **45**) or by resonance (**46**) effects, as illustrated in **Figure 4.1**.

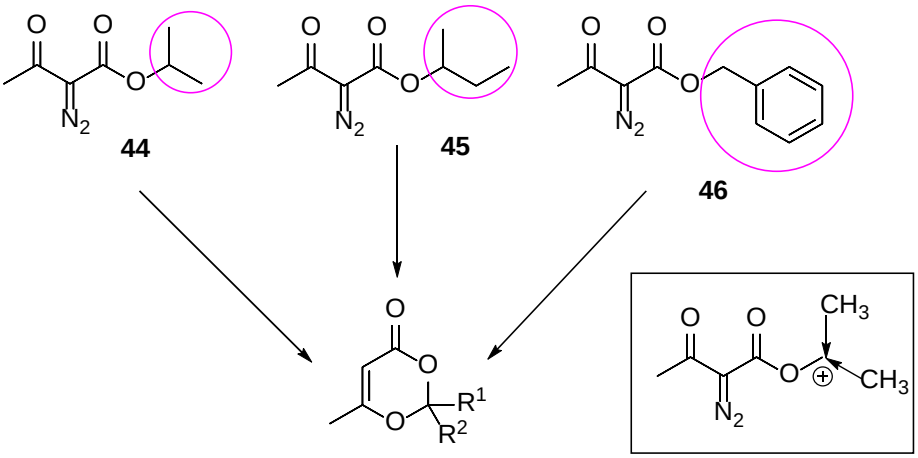
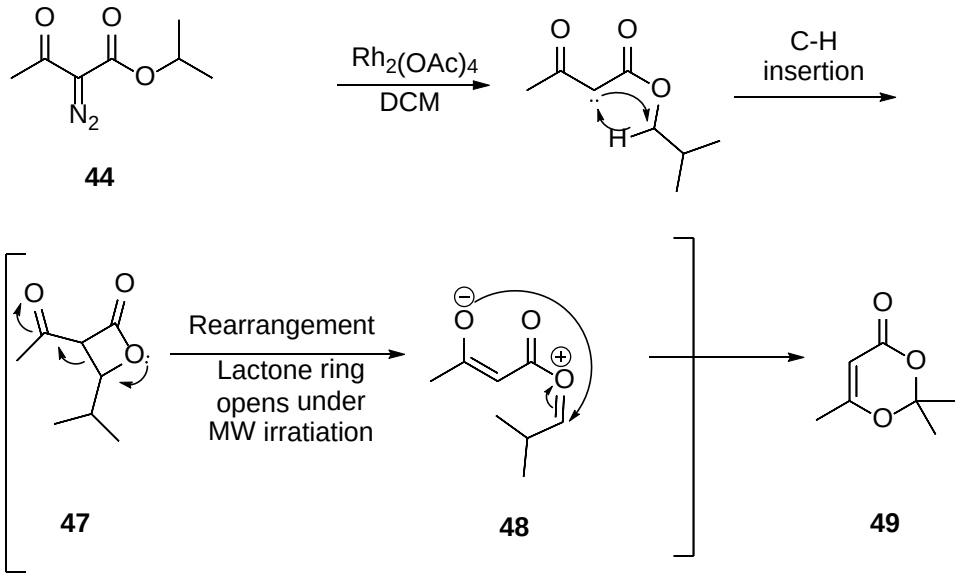


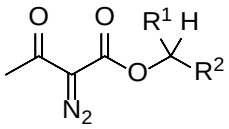
Figure 4.1 α-Diazo-β-ketoesters which have previously been shown to yield dioxinone products after rhodium(II) catalysed decomposition.

This rearrangement has been proposed to proceed *via* the mechanism shown below in **Scheme 4.2**. Following loss of nitrogen to generate the carbene, C-H insertion occurs to form the β-lactone **47**. This can then rearrange to the carbocation intermediate **48**, before subsequent nucleophilic attack of the enolate to give the dioxinone product **49**.



Scheme 4.2

With this in mind, the aim of this part of the project is to explore the scope of the extent to which electronic effects influence the formation of lactones versus dioxinones. This will be achieved by synthesis of a library of α-diazo-β-ketoesters of the general structure shown in **Figure 4.2**, where R^1 and R^2 represent groups that can stabilise the carbocation formed in the course of the rearrangement, either by inductive or resonance effects. These α-diazo-β-ketoesters will then be used in rhodium(II) catalysed decomposition reactions, and the products will be examined to determine the influence of electronic effects of R^1 and R^2.



R^1, R^2 = H, alkyl, aryl

$R^1 + R^2 \neq H$

Figure 4.2

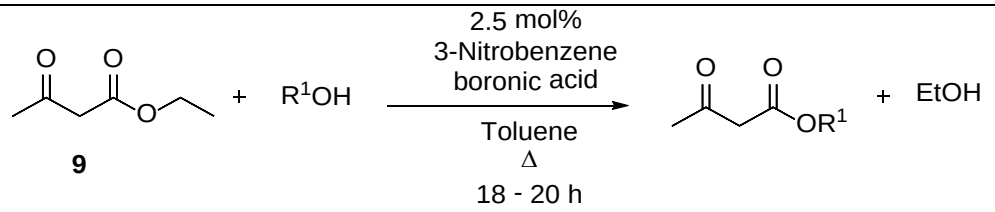
4.1.2 Design and synthesis of α-diazocarbonyl compounds

4.1.2.1 Preparation of ester derivatives

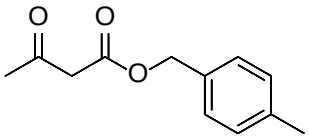
The transesterification method reported by Tale and Adude[2] previously discussed in **Section 2.2.1** was used to synthesise a range of non-commercially available β-ketoesters with the

desired structural features. Two derivatives were also synthesised which would not result in a stabilised carbocation following decomposition (**55** and **56**) due to the strongly electron withdrawing groups in the *para* position, in order to test this theory.

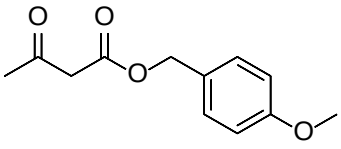
Table 4.1 ***Summary of β-ketoesters synthesised by transesterification***



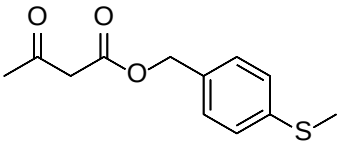
9



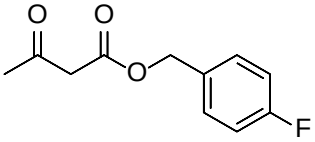
50
94 %



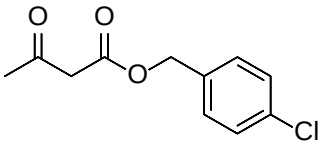
51
96 %



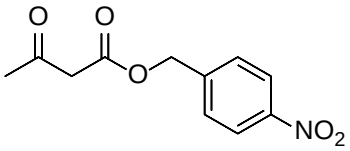
52
78 %



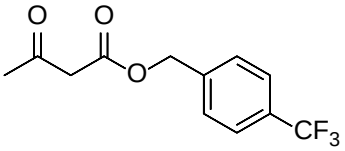
53
90 %



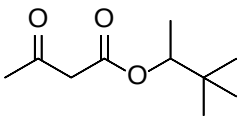
54
87 %



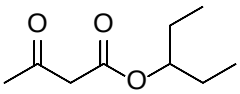
55
92 %



56
90 %



57
88 %



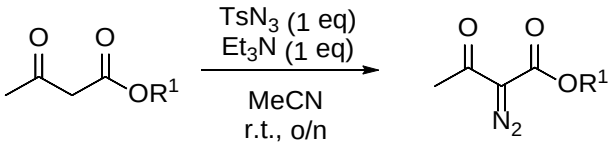
58
80 %

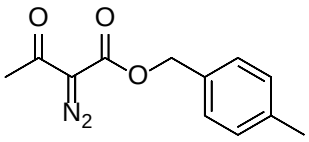
All α-diazo-β-ketoesters formed were isolated as clear or yellow oils, and were bench-stable over a period of several months. With the exception of **50**, all derivatives required purification by flash chromatography, and all were isolated in excellent yields. Perhaps due to the more complex alcohols employed to synthesise these derivatives in comparison to those made previously, longer reaction times were required for the transesterification reactions to go to completion.

4.1.2.2 Diazo Transfer to β-Ketoesters

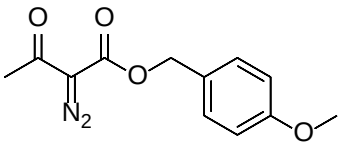
The adapted Regitz methodology outlined in **Section 2.2.3** was used to prepare a range of α-diazo-β-ketoesters. In addition to the nine non-commercially available β-ketoesters prepared as shown in **Table 4.1**, two commercially available esters were also used as starting materials (**Table 4.2**).

Table 4.2 ***Summary of α–diazo-β-ketoesters***

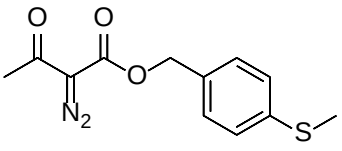




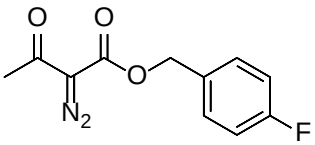
59
98 %



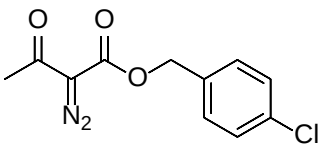
60
88 %



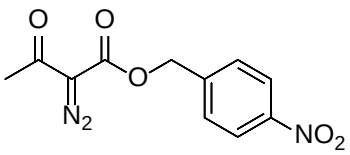
61
91 %



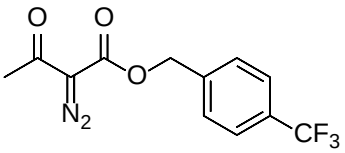
62
80 %



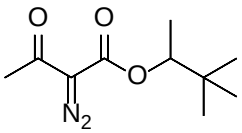
63
80 %



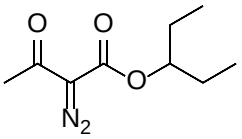
64
91 %



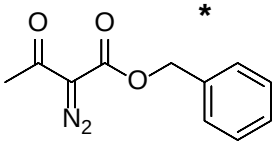
65
87 %



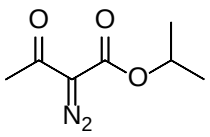
66
90 %



67
82 %



46
89 %



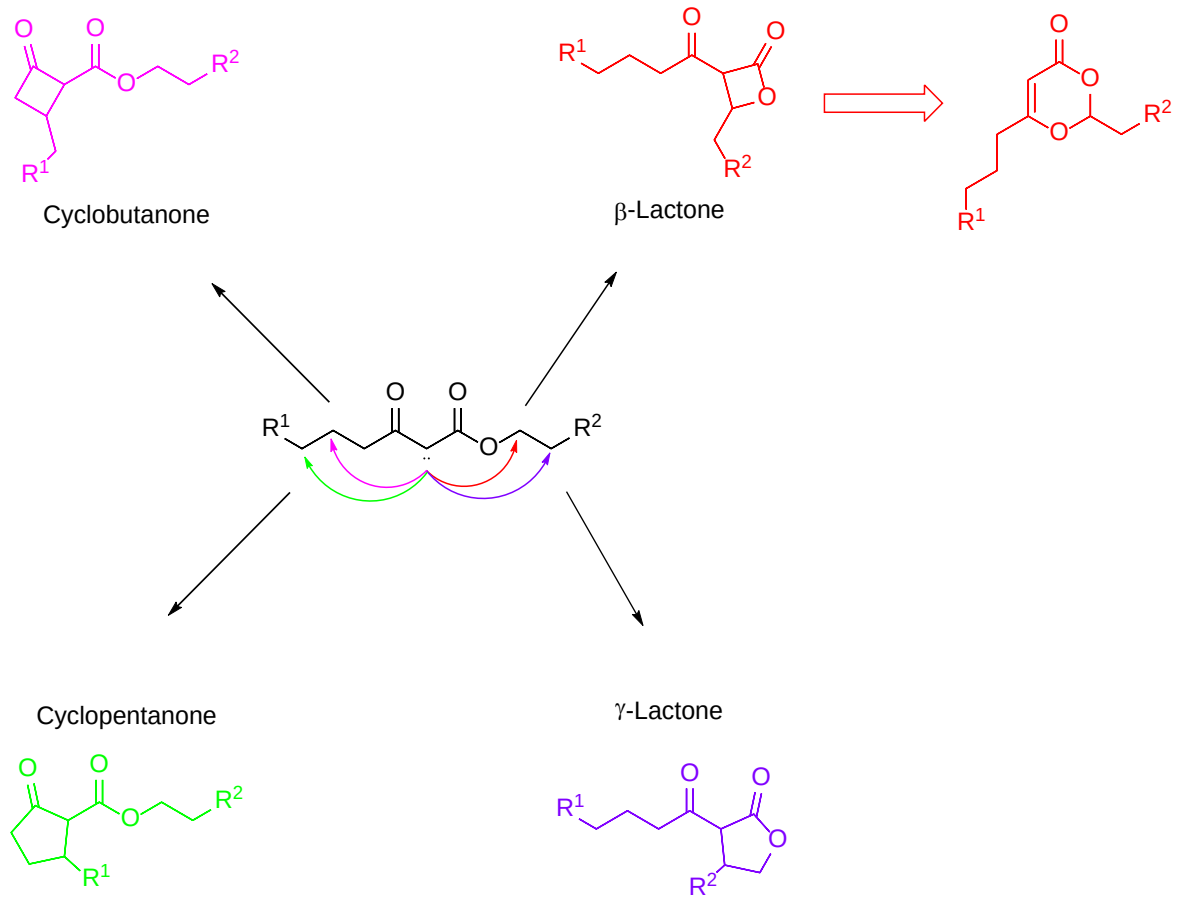
44
82 %

Compounds indicated with * were prepared from commercially available β-ketoesters.

Most of the benzyl side chain esters, **59**-**61** and **63**-**64**, were isolated as yellow solids, while the remainder were isolated as bright yellow oils. All diazo compounds synthesised were found to be shelf stable over a period of several months, and were isolated in high yields. In addition to this, following work-up of the crude reaction mixtures using 9% KOH washes, all compounds were isolated in high purity and could be used without further purification by flash chromatography.

Reaction monitoring for these reactions was carried out by TLC analysis, but typically an overnight reaction time was required. Following complete consumption of the β-ketoester starting material, the reaction mixture was worked up using a KOH wash and a ^{1}H NMR spectrum of the crude reaction mixture was obtained. Evidence for diazo transfer was characterised by the disappearance of the 2H singlet belonging to the methylene protons between the ester and the ketone in the range of δ_H 3.34-3.49 ppm, and the shift of the 3*H* singlet of the methyl ketone protons from approximately δ_H 2.25 ppm to approximately δ_H 2.45 ppm. In addition to this, there is a disappearance of a CH_2 signal in the ^{13}C NMR spectrum of the reaction mixture, although the quaternary carbon belonging to the $C=N_2$ group is typically not observed. The α-diazo-β-ketoesters are also characterised by absorptions in the IR spectra at approximately ν_{max} 2100 cm^{-1} ($C=N_2$ stretch) due to extended conjugation involving the diazo ($C=N_2$) group and carbonyl bonds.

While it is possible to alter the methyl ketone group to include longer alkyl chains and more interesting functionality such as aryl groups, ketones and alkenes, previous work within the group has shown that this can give rise to an additional competing C-H insertion reaction pathway when the diazo compound is subjected to decomposition, as illustrated below in **Scheme 4.3**.[1] Formation of dioxinones *via* the pathway shown below in red will be further discussed in **Section 4.1.4**.



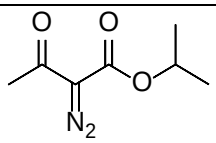
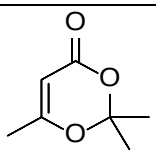
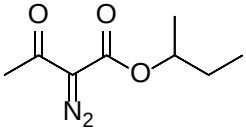
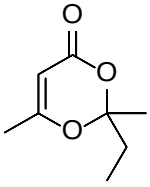
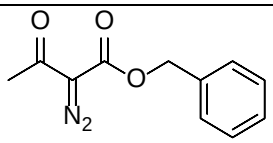
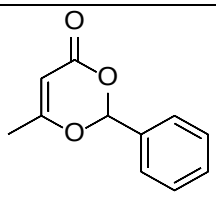
Scheme 4.3

4.1.3 Rh(II) catalysed decomposition reactions of α-diazo β-ketoesters

4.1.3.1 Background

Previous work carried out within the group by Tarrant reported the formation of dioxinones from the rhodium(II) catalysed decomposition of three particular α-diazo-β-ketoesters, as illustrated in **Figure 4.1**.[1] Tarrant tested several different reaction conditions for the synthesis of β-lactones, including varying reaction time, catalyst loading and heating method in the course of the research, and observed dioxinone formation only under certain conditions. The reaction conditions outlined in **Table 4.3** were used as a template going forward in the course of this project, which aimed to synthesise a library of dioxinones.

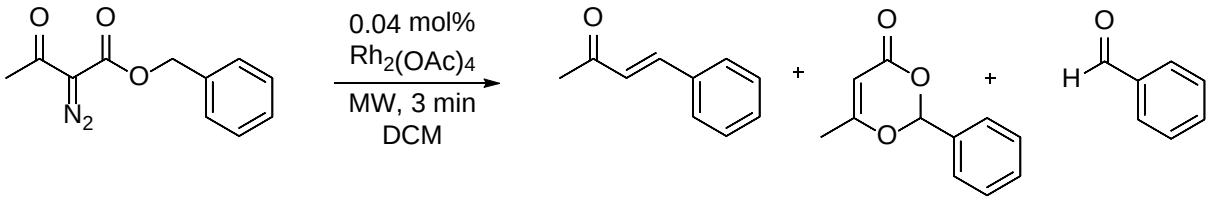
Table 4.3 ***Conditions which gave dioxinone formation in previous research***

Starting material	*Reaction Conditions*	*Dioxinone Formed*	*Yield*
 **44**	Reflux, 40 °C, 5 mol% $Rh_2(OAc)_4$, DCM, 1h <u>*or*</u> Microwave, 100 °C, 0.04 mol% $Rh_2(OAc)_4$, DCM, 3 mins	 **49**	Not isolated 29%
 **45**	Reflux, 40 °C, 5 mol% $Rh_2(OAc)_4$, DCM, 1h <u>*or*</u> Microwave, 100 °C, 0.04 mol% $Rh_2(OAc)_4$, DCM, 3 mins	 **68** Crude material only	Not isolated Not isolated
 **46**	Microwave, 100 °C, 0.04 mol% $Rh_2(OAc)_4$, DCM, 3 mins	 **69**	35%

4.1.3.2 Decomposition of benzyl 2-diazo-3-oxobutanoate **46**

Benzyl 2-diazo-3-oxobutanoate **46** was the first derivative subjected to rhodium decomposition. Rhodium acetate was used as the transition metal catalyst to promote decomposition, and the reaction was carried out under microwave irradiation at 100 °C for 3 minutes to give the following proposed products, as illustrated in **Scheme 4.4**. 0.04 mol% of rhodium(II) acetate was used as catalyst. This loading was chosen as previous work within the group had determined that a vastly reduced catalyst loading of 0.04 mol% is sufficient to

facilitate the reaction under microwave conditions, but 5 mol% catalyst is required to induce decomposition at room temperature or under reflux.[1]



46 **70** **69** **71**

Ratio in ^{1}H NMR spectrum of crude mixture:	5	:	3	:	1
Isolated Yield:	28%		13%		not isolated

Scheme 4.4

The ^{1}H NMR spectrum of the crude reaction mixture is shown in spectrum (b) in **Figure 4.2**. As can be seen below, the crude reaction mixture contains a complex mixture of decomposition products and shows characteristic peaks for **69**, **70** and **71**. Following repeated careful column chromatography on silica gel, two fractions were isolated. Based on previous work carried out within the group, these were identified as (*E*)-4-phenylbut-3-en-2-one **70** and 6-methyl-2-phenyl-4H-1,3-dioxin-4-one **69**, as shown in **Scheme 4.4**. It should be noted that several other fractions were collected but contained unidentifiable decomposition products. A peak at δ_H 10 ppm in the ^{1}H NMR spectrum of the crude reaction mixture was believed to correspond to benzaldehyde **71**, but this was not isolated following column chromatography. Subsequent work on other derivatives confirmed that the relevant aldehyde, in this case benzaldehyde, is formed as a decomposition product.

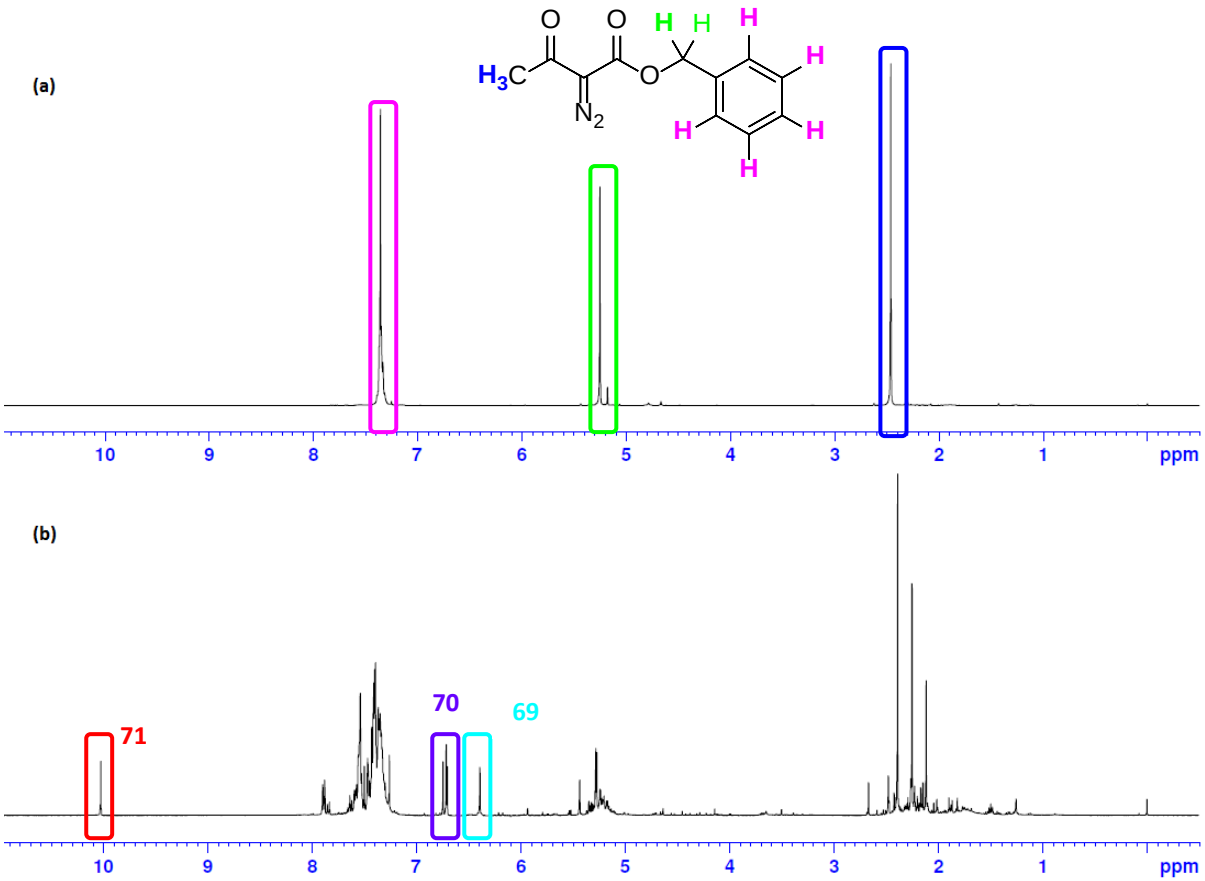


Figure 4.2 (a) ^{1}H NMR spectrum of benzyl 2-diazo-3-oxobutanoate **46** (b) ^{1}H NMR spectrum of the crude reaction mixture for the following reaction: 1 eq. benzyl 2-diazo-3-oxobutanoate **46** with 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation for 3 mins at 100 °C.

(*E*)-4-Phenylbut-3-en-2-one **70** was also isolated as the major product from the crude reaction mixture described above. As can be seen in **Scheme 4.5**, the yields of these decomposition products are quite low, however this is not unexpected due to the presence of other unidentifiable decomposition products.

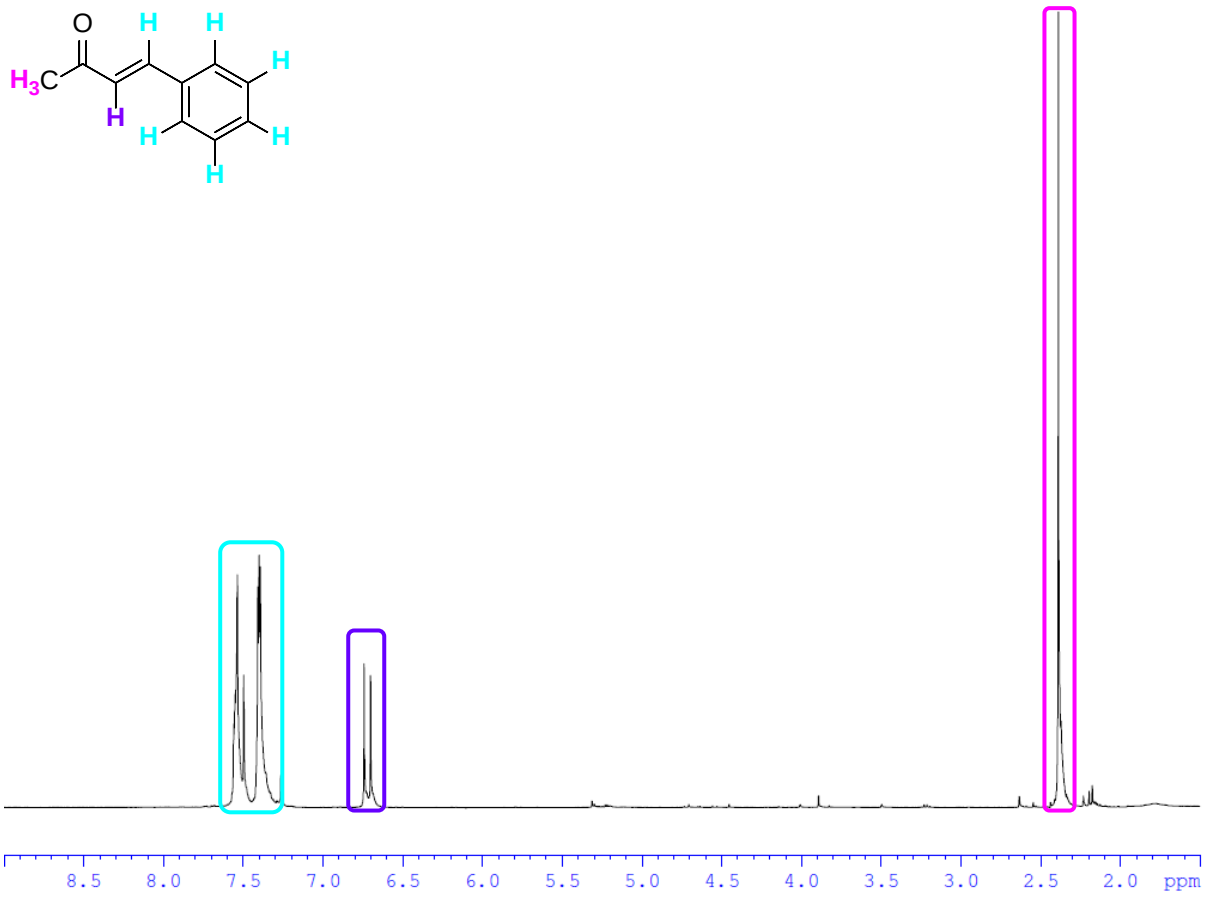


Figure 4.3 ^{1}H NMR spectrum of (*E*)-4-phenylbut-3-en-2-one **70.**

The ^{1}H NMR spectrum of (*E*)-4-phenylbut-3-en-2-one **70** is shown in **Figure 4.3** above. As can be seen below, the 1H doublet at δ_H 6.72 ppm corresponds to the alkene proton alpha to the carbonyl, while the other alkene proton appears in the same region as the aromatic protons. **70** is a known compound in the literature, and all spectral details are consistent with those previously reported.[3] This distinctive doublet at δ_H 6.72 ppm is characteristic of all alkenes synthesised *via* rhodium(II) decomposition of a-diazo-carbonyl compounds in the course of this project, and can therefore be used to indicate the presence of these products in the complex ^{1}H NMR spectra which result from these decomposition reactions.

Figure 4.4 shows the ^{1}H NMR spectrum of 6-methyl-2-phenyl-4H-1,3-dioxin-4-one **69**. Distinctive signals associated with this compound include two singlets at δ_H 5.43 ppm and 6.39 ppm. Interestingly, in the dioxinone, the alkene proton appears further upfield in the ^{1}H

NMR spectrum compared to the alkene protons in **70**. This is due to the deshielding effect of the phenyl ring in **70**.

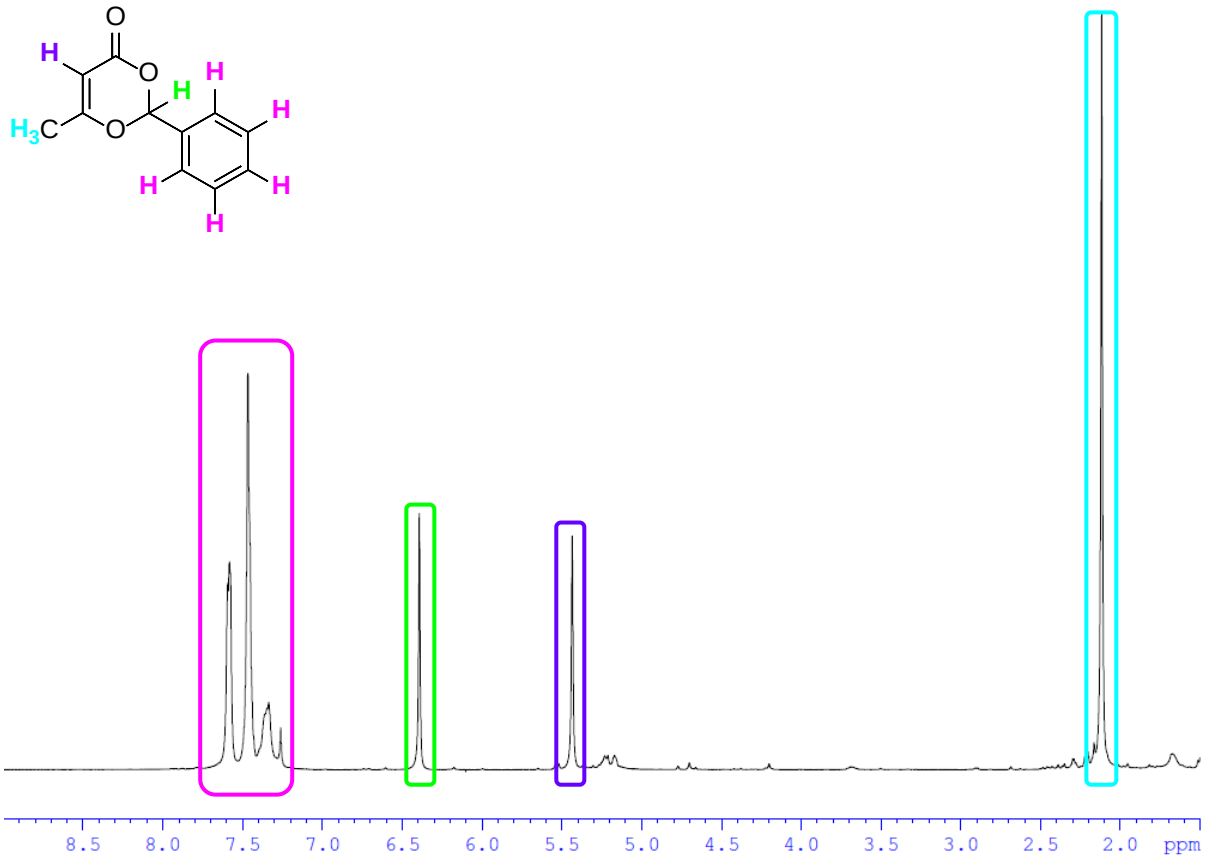
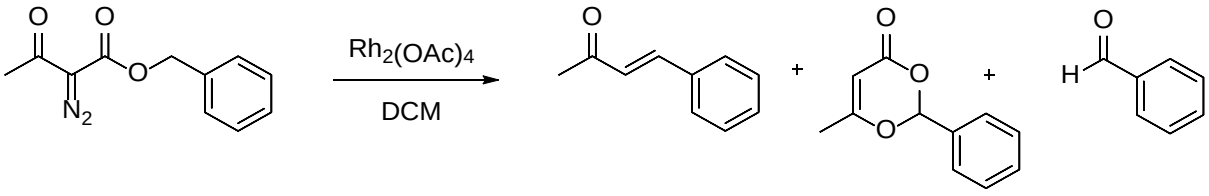


Figure 4.4 ^{1}H NMR spectrum of 6-methyl-2-phenyl-4H-1,3-dioxin-4-one **69.**

The characteristic signals outlined above for 6-methyl-2-phenyl-4H-1,3-dioxin-4-one **69** and (*E*)-4-phenylbut-3-en-2-one **70** allow us to calculate the ratio of these products in the ^{1}H NMR spectra of the crude reaction mixtures, as shown in **Table 4.4**. As can be seen below, evidence for **69** was observed only when the reaction was carried out under microwave irradiation. **70** was observed in all cases, and following column chromatography of the crude reaction mixtures, was isolated in each case in small yields. The mechanism of formation of these products will be discussed in more detail in **Section 4.1.4**.

Table 4.4 ***Decomposition of 46 using $Rh_2(OAc)_4$ in DCM***

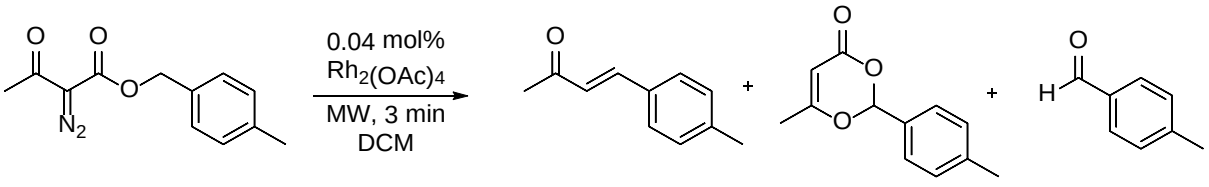


46 **70** **69** **71**

Entry	$Rh_2(OAc)_4$ Loading (mol%)	Conditions	Time	Crude Product Ratio 70 : 69 : 71
1	5	RT	18 h	4 : 0 : 3
2	5	Δ (40 °C)	1.5 h	1 : 0 : 1
3	0.04	MW (100 °C)	3 min	5 : 3 : 1

4.1.3.3 Decomposition of 4-methylbenzyl 2-diazo-3-oxobutanoate **59**

4-Methylbenzyl 2-diazo-3-oxobutanoate **59** was subjected to decomposition in the presence of rhodium(II) acetate, and the reaction was carried out under microwave irradiation at 100 °C for 3 minutes, as illustrated in **Scheme 4.5**.



59 **72** **73** **74**

Ratio in ^{1}H NMR spectrum of crude mixture:	3	:	3	:	2
Isolated Yield:	16%		17%		not isolated

Scheme 4.5

The ^{1}H NMR spectrum of the crude reaction mixture showed no evidence of unreacted 4-methylbenzyl 2-diazo-3-oxobutanoate **59** remaining, and the crude reaction mixture contains a complex mixture of products. The characteristic peaks corresponding to (*E*)-4-(*p*-tolyl)but-3-en-2-one **72**, 6-methyl-2-(*p*-tolyl)-4H-1,3-dioxin-4-one **73** and 4-methylbenzaldehyde **74** were used to determine the ratio of alkene to dioxinone to aldehyde present in the crude reaction mixture as 3:3:2, as shown below in **Figure 4.5**. The alkenes formed in the course of this research were assigned as *trans* based on the J values of the alkene protons, which were typically ~16 Hz.

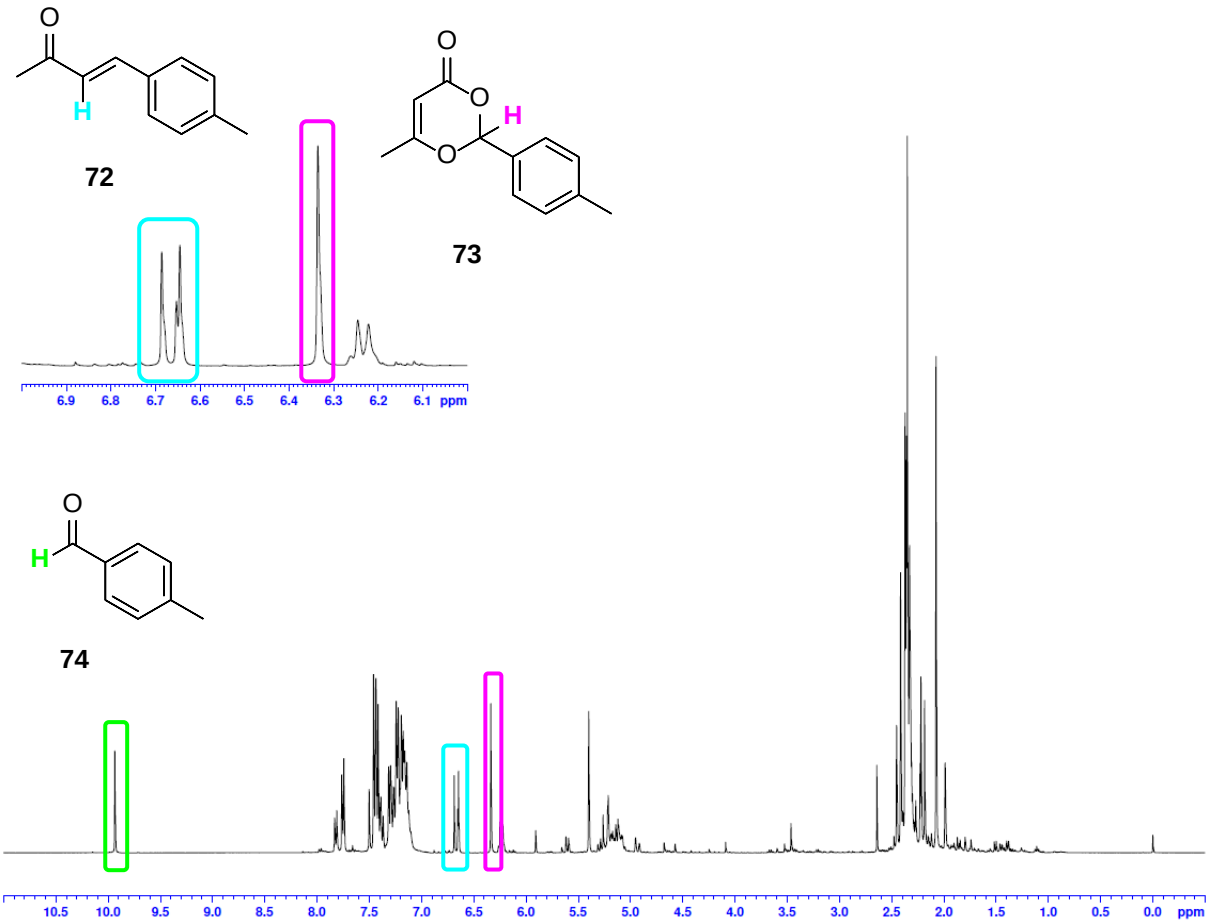
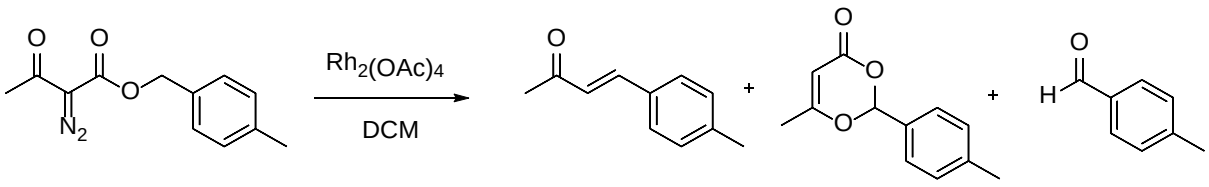


Figure 4.5 ^{1}H NMR spectrum the crude reaction mixture for the following reaction: 1 eq. 4-methylbenzyl 2-diazo-3-oxobutanoate **59** with 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation for 3 mins at 100 °C.

Following careful column chromatography on silica gel, (*E*)-4-(*p*-tolyl)but-3-en-2-one **72** and 6-methyl-2-(*p*-tolyl)-4H-1,3-dioxin-4-one **73** were isolated in low yields. 4-methylbenzaldehyde **74** was not isolated following column chromatography. Rhodium(II) decompositions of 4-methylbenzyl 2-diazo-3-oxobutanoate **59** were also carried out at room temperature and using conventional heating, the results of which are summarised in **Table 4.5** below. Interestingly, 6-methyl-2-(*p*-tolyl)-4H-1,3-dioxin-4-one **73** was observed, and later isolated from the crude reaction mixture of a reflux decomposition reaction. Although previous work within the group reported formation of alkyl dioxinones from reflux decomposition reactions, this is the first case of a benzyl dioxinone forming without microwave irradiation.

Table 4.5 ***Decomposition of 59 using $Rh_2(OAc)_4$ in DCM***



59 **72** **73** **74**

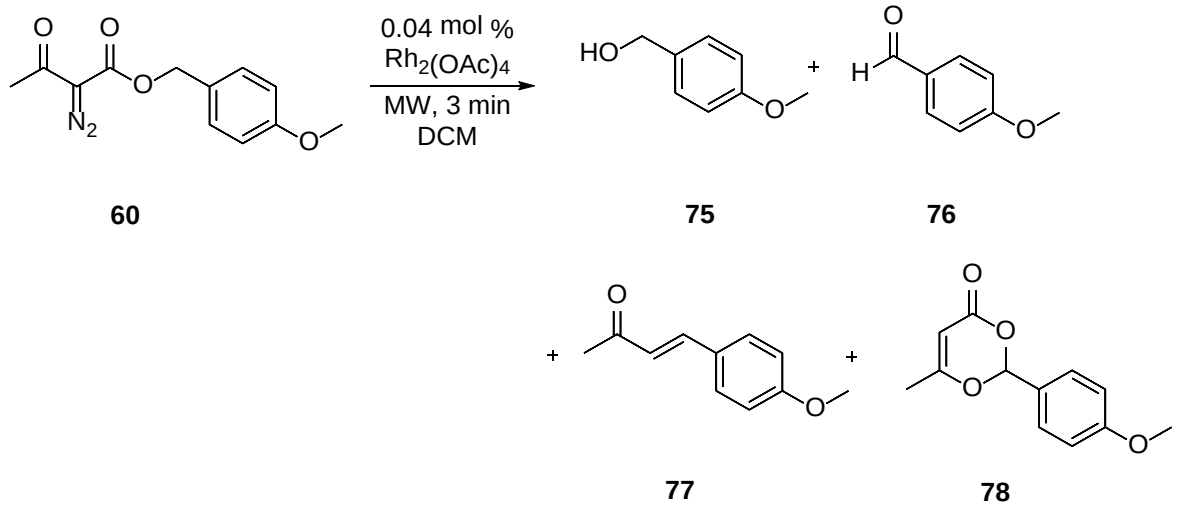
Entry	$Rh_2(OAc)_4$ Loading (mol%)	Conditions	Time	Crude Product Ratio 72 : 73 : 74
1	5	RT	18 h	1 : 0 : 2
2	5	Δ (40 °C)	1.5 h	5 : 3 : 10
3	0.04	MW (100 °C)	3 min	3 : 3 : 2

As can be seen above, evidence for the formation of 4-methylbenzaldehyde **74** was observed in all cases, and it is in fact the major component of the crude reaction mixture following decomposition at both reflux and room temperatures. Despite this **74** was not isolated from any of the crude reaction mixtures, even after repeated column chromatography of fractions

containing **74** and other decomposition products. Interestingly, (*E*)-4-(*p*-tolyl)but-3-en-2-one **72** was formed in the most significant amount under reflux conditions.

4.1.3.4 Decomposition of 4-methoxybenzyl 2-diazo-3-oxobutanoate **60**

4-Methoxybenzyl 2-diazo-3-oxobutanoate **60** was heated to 100 °C under microwave conditions in the presence of 0.04 mol% rhodium(II) acetate. When the ^{1}H NMR spectrum of the crude reaction mixture was obtained, characteristic peaks for **75**, **76**, **77** and **78** were observed, as shown in **Scheme 4.6**.



60 **75** **76** **77** **78**

	75	**76**	**77**	**78**
Ratio in ^{1}H NMR spectrum of crude mixture:	1:	5:	2:	5
Isolated yield:	9%	10%	not isolated	20%

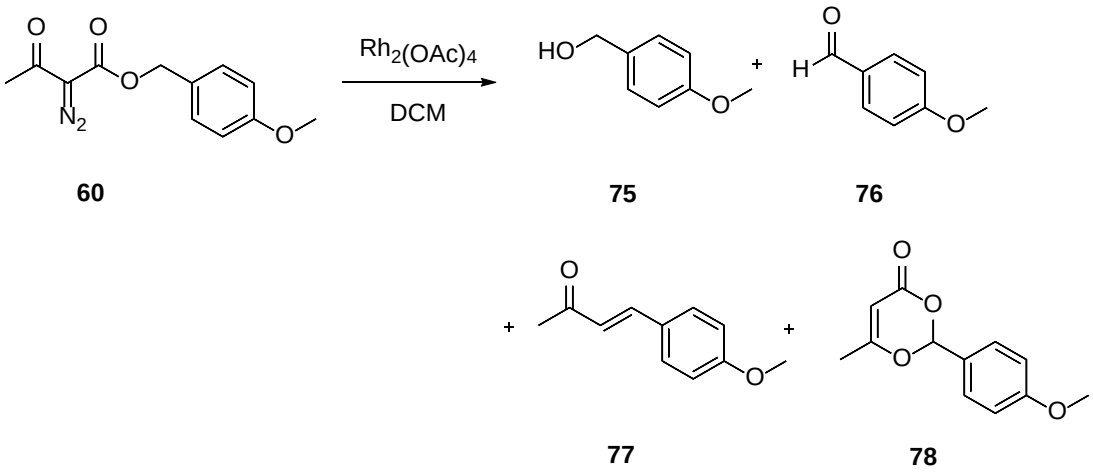
Scheme 4.6

Following flash chromatography, three compounds were isolated from the reaction mixture. The first fraction contained 4-methoxybenzaldehyde **76**. A peak at approximately δ_H 10 ppm has been observed in the ^{1}H NMR spectrum of all crude reaction mixtures to date, however this is the first time the compound has been isolated. A detailed mechanistic exploration will be discussed in **Section 4.1.4**.

2-(4-Methoxyphenyl)-6-methyl-4H-1,3-dioxin-4-one **78** was also isolated from the crude reaction mixture, in an increased yield of 20% compared to previous derivatives. A small quantity of 4-methoxybenzyl alcohol **75** was isolated from the reaction mixture.

Table 4.6 summarises the results obtained when 4-methoxybenzyl 2-diazo-3-oxobutanoate **60** was subjected to rhodium(II) catalysis under various reaction conditions. As can be seen below, 4-methoxybenzaldehyde **76** continues to be the major component of the reaction mixture. 2-(4-Methoxyphenyl)-6-methyl-4H-1,3-dioxin-4-one **78** was observed, and later isolated, from the crude reaction mixtures of both the reflux and microwave decomposition reactions.

Table 4.6 ***Decomposition of 60 using $Rh_2(OAc)_4$ in DCM***



60 **75** **76** **77** **78**

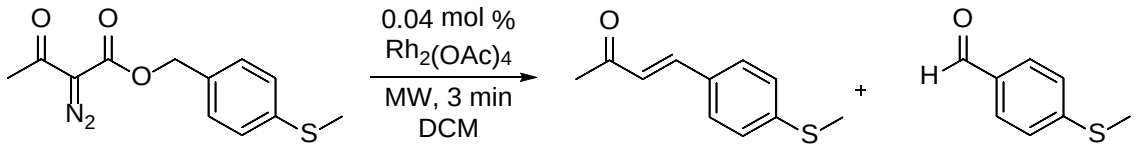
Entry	$Rh_2(OAc)_4$ Loading (mol%)	Conditions	Time	Crude Product Ratio 75 : 76 : 77 : 78
1	5	RT	18 h	0 : 10 : 1 : 0
2	5	Δ (40 °C)	1.5 h	0 : 5 : 1 : 2
3	0.04	MW (100 °C)	3 min	1 : 5 : 2 : 5

When the relative amount of **76** in each reaction mixture is compared, it can be seen that a significantly larger quantity is formed at room temperature when compared to the other reaction conditions. It should also be noted that this is the first substrate which does not result

in the formation of the alkene as a major product. Although **77** is present in each reaction mixture, it is present in very small quantities relative to **76** and **78**. Gratifyingly, **78** is a major component of the microwave irradiation reaction, in keeping with the results obtained from other substrates examined so far.

4.1.3.5 Decomposition of 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61**

When the rhodium(II) catalysed decomposition of 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** was done under microwave irradiation, a purple solution was obtained. The ^{1}H NMR sample of the crude reaction mixture showed no evidence of dioxinone formation, therefore 5 mol% of rhodium(II) acetate was added to the sample, which was subjected to a further 3 minutes under microwave conditions.



61 **79** **80**

Ratio in ^{1}H NMR spectrum of crude mixture:	3	:	4
Isolated Yield:	16%		10%

Scheme 4.7

The ^{1}H NMR sample of the crude reaction mixture after 3 and 6 minutes are shown in **Figure 4.6** below. As can be seen, even after additional reaction time with increased catalyst loading there is no evidence of dioxinone formation, as evidenced by the lack of the distinctive 1H singlet at approximately δ_H 6.3 ppm which is characteristic of dioxinones. This was unexpected as 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** is analogous to 4-

methoxybenzyl 2-diazo-3-oxobutanoate **60**, which did form 2-(4-methoxyphenyl)-6-methyl-4H-1,3-dioxin-4-one **78** in 20% yield under microwave irradiation (**Section 4.1.3.4**).

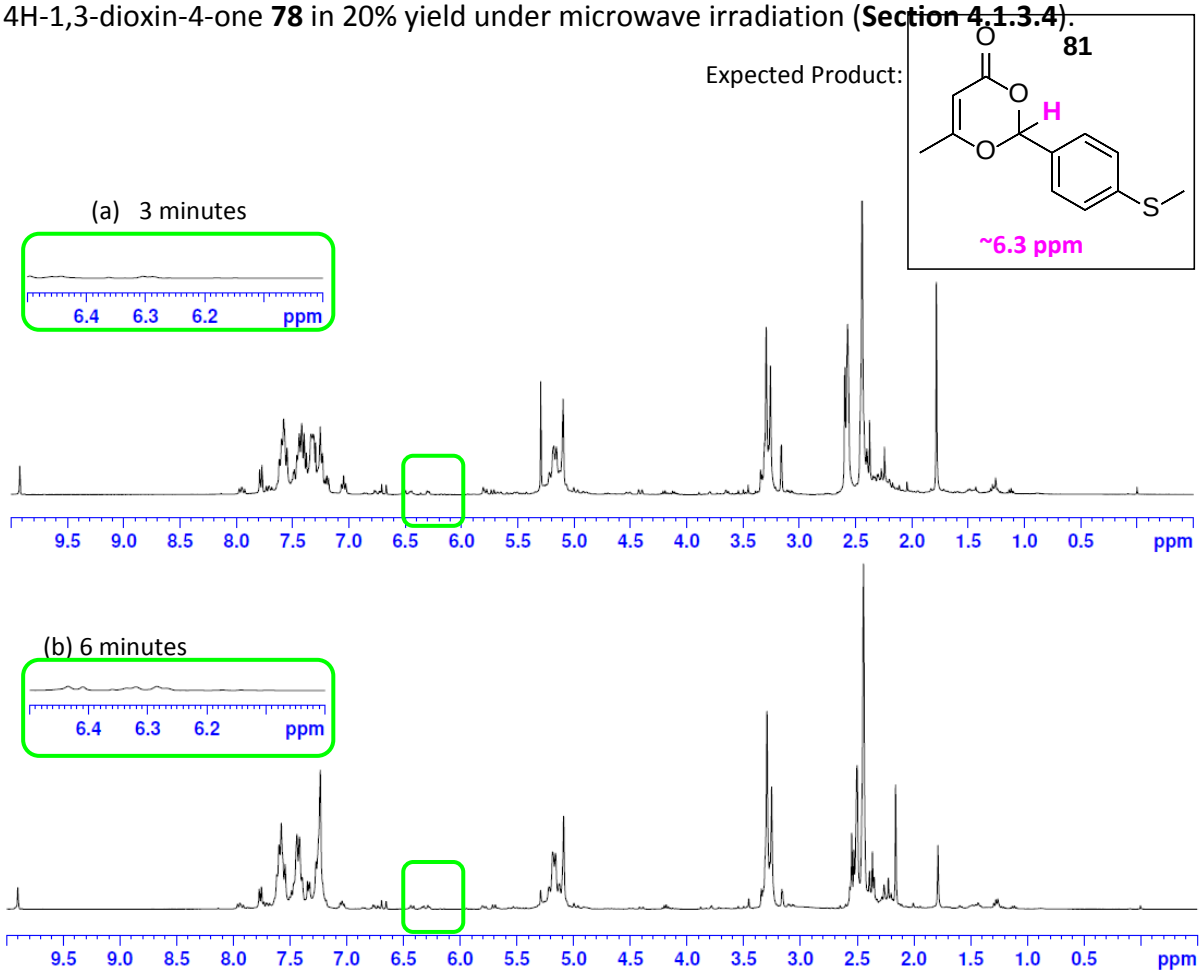


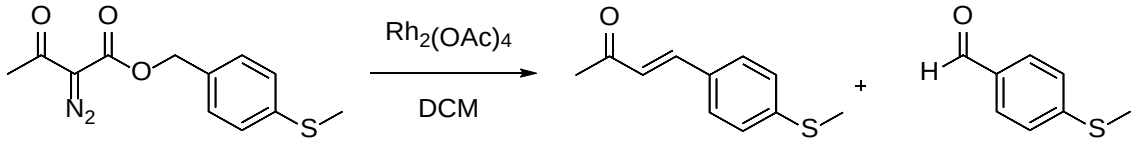
Figure 4.6 ^{1}H NMR spectra the crude reaction mixtures for the following reactions: (a) 1 eq. 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** with 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation for 3 mins at 100 °C, (b) 1 eq. 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** with 5 mol % $Rh_2(OAc)_4$ under MW irradiation for 6 mins at 100 °C.

Following column chromatography of the crude reaction mixture on silica gel, 4-(methylthio)benzaldehyde **80** and the novel alkene (*E*)-4-(4-(methylthio)phenyl)but-3-en-2-one **79** were isolated, as illustrated in **Scheme 4.7**.

Table 4.7 below, summarises the results of experiments carried out with 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61**. Unfortunately, when **61** was exposed to rhodium(II) acetate under conventional heating, or at room temperature, there was no evidence for the formation of dioxinone formation either. Although the distinctive 1H doublet of **79** was

observed in the ^{1}H NMR spectra of all reaction mixtures, it was only isolated in the case of the reaction under microwave irradiation.

Table 4.7 ***Decomposition of 61 using $Rh_2(OAc)_4$ in DCM***



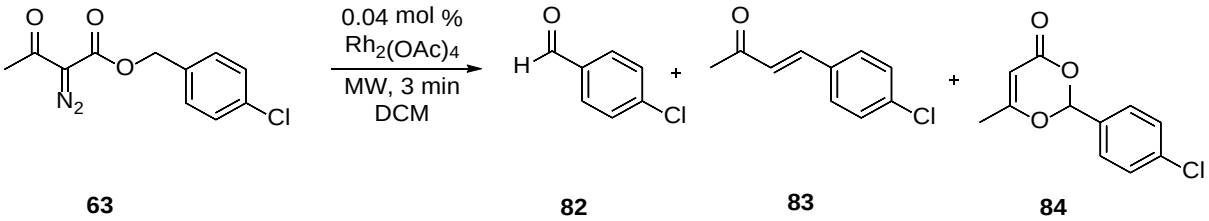
61 **79** **80**

Entry	$Rh_2(OAc)_4$ Loading (mol %)	Conditions	Time	Crude Product Ratio 79 : 80
1	5	RT	18 h	1 : 2
2	5	Δ (40 °C)	1.5 h	3 : 4
3	0.04	MW (100 °C)	3 min	3 : 4
4	5	MW (100 °C)	6 min	3 : 4

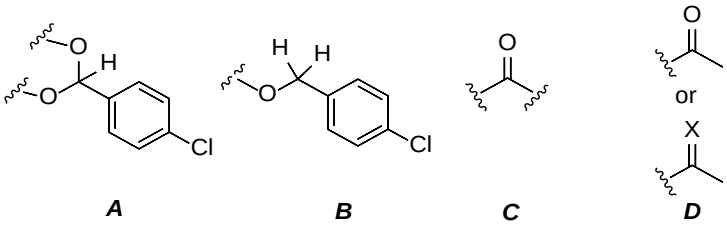
As can be seen above, 4-(methylthio)benzaldehyde **80** was the major product in all cases. It was isolated from the crude reaction mixtures in each case, in yields as high as 30% for Entry 2 above. This is the highest isolated yield of any decomposition product formed from these rhodium(II) decompositions.

4.1.3.6 Decomposition of 4-chlorobenzyl 2-diazo-3-oxobutanoate **63**

4-Chlorobenzyl 2-diazo-3-oxobutanoate **63** was heated under microwave conditions in the presence of rhodium(II) acetate for 3 minutes. The ^{1}H NMR spectrum of the crude reaction mixture showed evidence of (*E*)-4-(4-chlorophenyl)but-3-en-2-one **83**, 2-(4-chlorophenyl)-6-methyl-4H-1,3-dioxin-4-one **84** and 4-chlorobenzaldehyde **82** and an unidentified compound **85**, as illustrated in **Scheme 4.8.**



63 **82** **83** **84**



	82	**83**	**84**	**85**
Ratio in ^{1}H NMR spectrum of crude mixture:	10:	7:	3:	9
Isolated yield:	not isolated	18%	10%	-[1]

[1] 102 mg mass yield from 490 mg **63**.

Scheme 4.8

Following column chromatography on silica gel, (*E*)-4-(4-chlorophenyl)but-3-en-2-one **83**, 2-(4-chlorophenyl)-6-methyl-4H-1,3-dioxin-4-one **84**, along with a third unknown compound **85** were isolated. 4-Chlorobenzaldehyde **82** could not be isolated although the ^{1}H NMR of several fractions showed singlets at δ_H 10 ppm.

The ^{1}H NMR spectrum of the unknown compound **85** isolated from the above reaction (b), along with the ^{1}H NMR spectra of **63** (a) and **84** (c) are shown below. As can be seen in **Figure 4.7**, a 3H singlet is observed at δ_H 2.24 ppm with a 2H apparent quartet at δ_H 5.23 ppm. There is also a 1H singlet at δ_H 6.69 ppm, and an 8H multiplet in the aromatic region of the spectrum, at δ_H 7.26-7.50 ppm.

By comparing the observed signals to those seen for **63** and **84** we can determine that the methyl group observed in the ^{1}H NMR spectrum of **85** is in a different electronic environment, as it appears at δ_H 2.24 ppm compared to δ_H 2.45 ppm in **63** and δ_H 2.12 ppm in **84**. In addition

to this, the methyl group is seen at δ_C 11.5 ppm in the ^{13}C NMR spectrum, compared to δ_C 28.2 ppm in **63** and δ_C 19.6 ppm in **84**. Based on these values, it is likely that the methyl group is directly attached to an sp^2 hybridised carbon, perhaps a carbonyl or an alkene, as illustrated in **Scheme 4.8** (Fragment **D**).

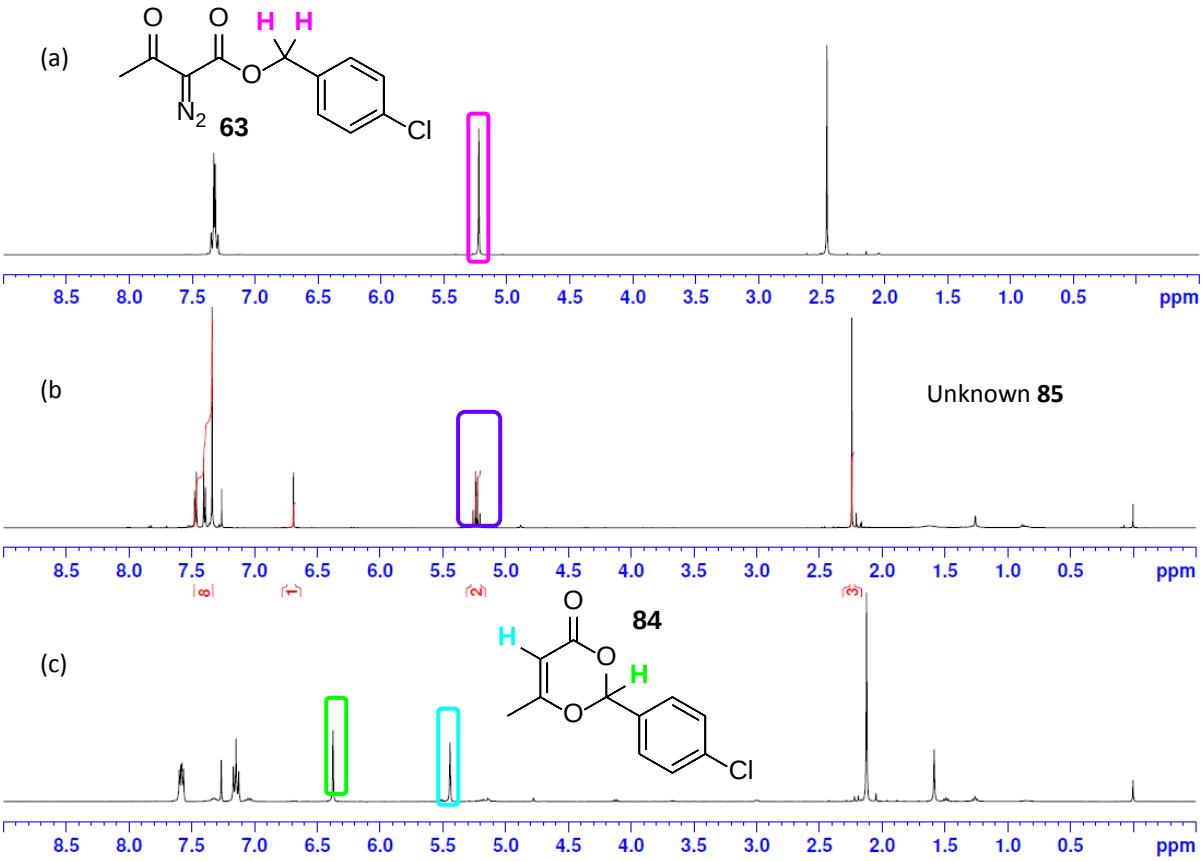


Figure 4.7 (a) ^1H NMR spectrum of 4-chlorobenzyl 2-diazo-3-oxobutanoate **63, (b)** ^1H NMR spectrum of unknown **85**, (c) ^1H NMR spectrum of 2-(4-chlorophenyl)-6-methyl-4H-1,3-dioxin-4-one **84.**

A HSQC NMR experiment was used in an attempt to clarify the structure of **85**. This is shown below in **Figure 4.8**. The apparent 2H quartet observed at δ_H 5.23 ppm corresponds to a CH_2 group in a very electron-rich environment, and as shown below, the signal corresponding to this appears at δ_C 65.5 ppm in the ^{13}C NMR spectrum, compared to δ_C 66 ppm in **63**. **84** also has a signal at δ_H 5.44 ppm as highlighted in purple in **Figure 4.7**, however the corresponding signal in the ^{13}C NMR is very different from **85**, appearing at δ_C 96.6 ppm. This suggests that

the CH_2 group in **85** is in a very similar environment to the CH_2 group in **63** as shown by Fragment B in **Scheme 4.8**, however this does not explain the splitting of the two protons into an apparent quartet unless they are diastereotopic.

Finally, the 1H singlet at δ_H 6.69 ppm correlates to the CH signal at δ_C 107.1 ppm in the ^{13}C NMR spectrum as can be seen in **Figure 4.8**. These signals are very similar to the proton marked in green above in **84**, which appears at δ_H 6.36 ppm in the ^{1}H NMR spectrum and at δ_C 99.4 ppm in the ^{13}C NMR spectrum, as shown by Fragment A in **Scheme 4.8**.

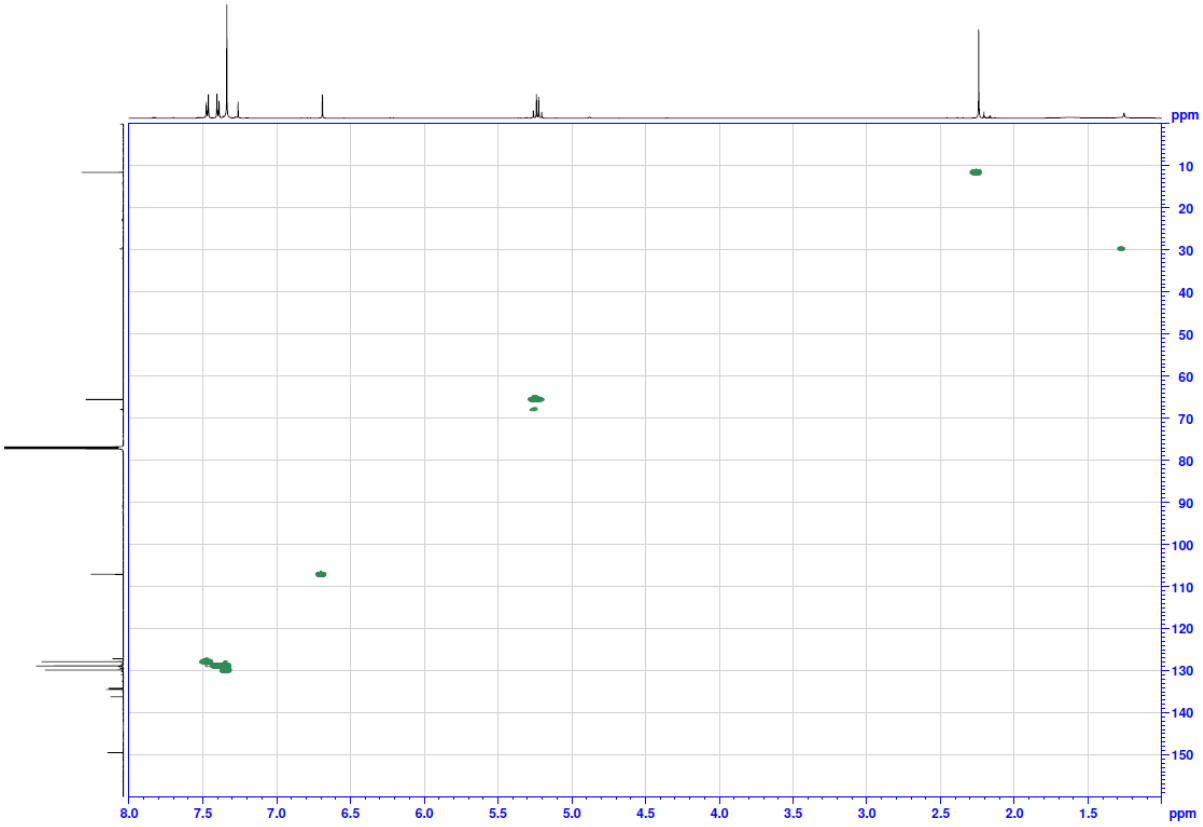
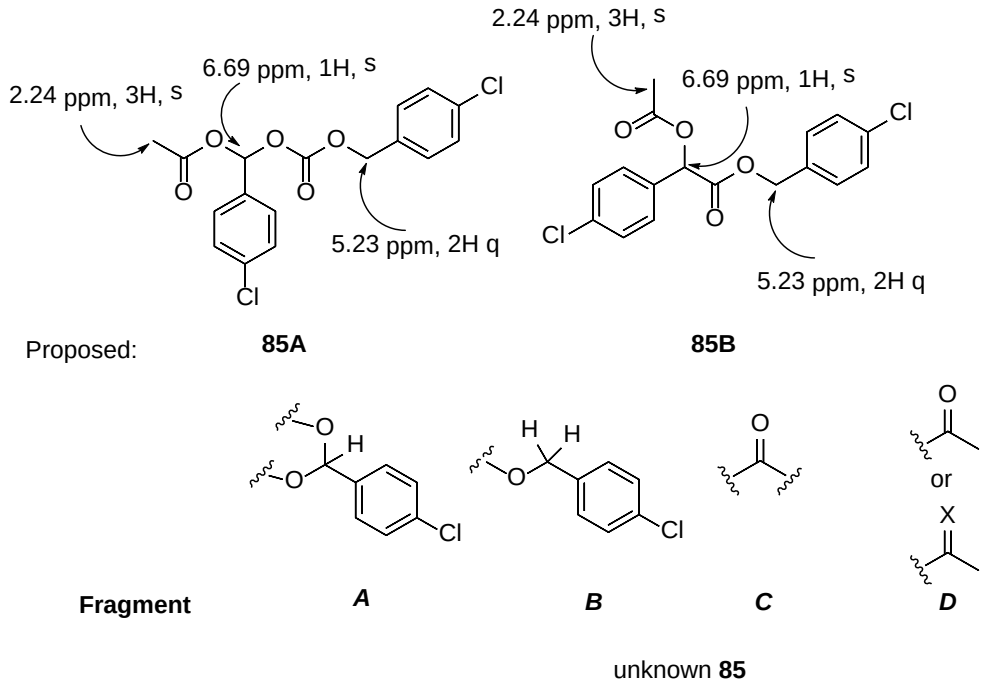


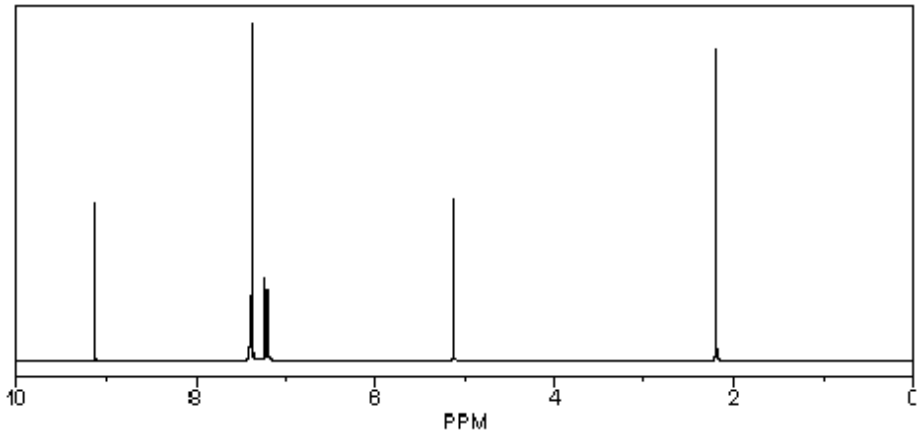
Figure 4.8 HSQC spectrum of **85.**

From the ^{13}C NMR we can also determine that a carbonyl is present, as indicated by the presence of a signal at δ_C 160.2 ppm. This is most likely an ester or carboxylic acid carbonyl group. Future work will further investigate this reaction product to try and determine the exact structure of the compound.

Based on these observations, the structures outlined in **Figure 4.9** are tentatively proposed. As can be seen below, **85A** and **85B** differ only because **85A** has an ester group and a carbonate group, while **85B** has two ester groups.



(a) ChemDraw ^{1}H NMR prediction – **85A**



(b) ChemDraw ^{1}H NMR prediction – **85B**

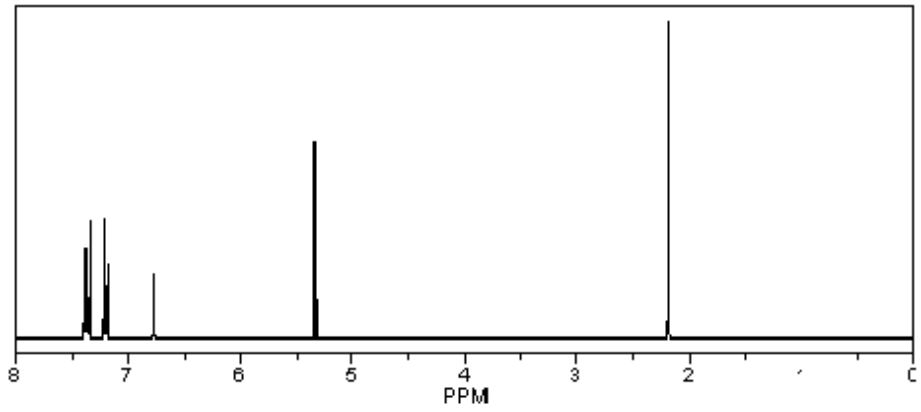


Figure 4.9 Tentatively proposed structures for **85**.

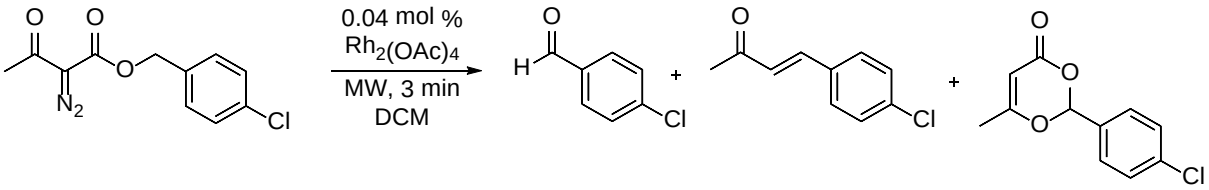
Figure 4.9 shows the estimations for ^{1}H NMR values for **85A** and **85B** as determined by the ChemBioDraw software package. As can be seen above, the estimation for **85B** is a very good fit for the ^{1}H NMR of **85** shown in **Figure 4.7**, pg. 264. However the estimation for **85A** is also a good match, except for the peak at δ_H 9.2 ppm, corresponding to H between the ester and carbonate functional groups (shown in Fragment **A**). Although this is predicted to be at δ_H 9.2 ppm, we know from the ^{1}H NMR spectrum of the dioxinone product **84** that a proton in this environment is actually observed in the region of δ_H 6.7 ppm. The fragments outlined above could therefore correspond to either structure, however nominal mass spectrometry analysis has proved inconclusive at this point. Further work is required to conclusively determine the correct structure of unknown **85**.

Arguably, **85B** is more likely from a structural viewpoint, as **85B** appears to be made up of two halves of the parent diazo compound **63**. A mechanism has not be determined to explain how

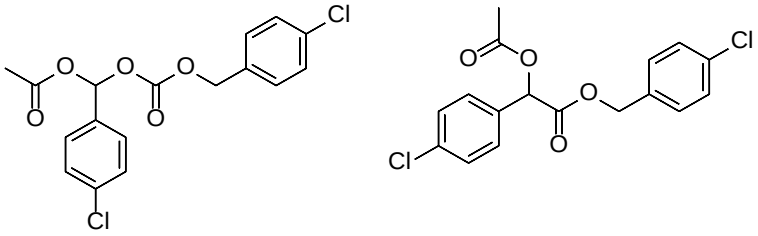
either compound might form, however it is more difficult to explain where the additional oxygen in the carbonate group of **85A** could come from.

When subsequent decomposition experiments were carried out with 4-chlorobenzyl 2-diazo-3-oxobutanoate **63** at reflux and room temperature both **82** and **83** were seen in the ^{1}H NMR of the crude reaction mixtures, although only **83** was recovered following column chromatography. Interestingly, although **85** was one of the major products from the decomposition reaction carried out in the microwave, signals attributed to it were not observed in the ^{1}H NMR spectra after the room temperature or reflux decomposition reactions. Evidence for the presence of **84** was also seen in the ^{1}H NMR spectrum of the crude reaction mixture of the reflux reaction, however it was not isolated under reflux conditions. These results are summarised in **Table 4.8**.

Table 4.8 ***Decomposition of 63 using $Rh_2(OAc)_4$ in DCM***



63 **82** **83** **84**



Proposed: **85A** or **85B**

unknown **85**

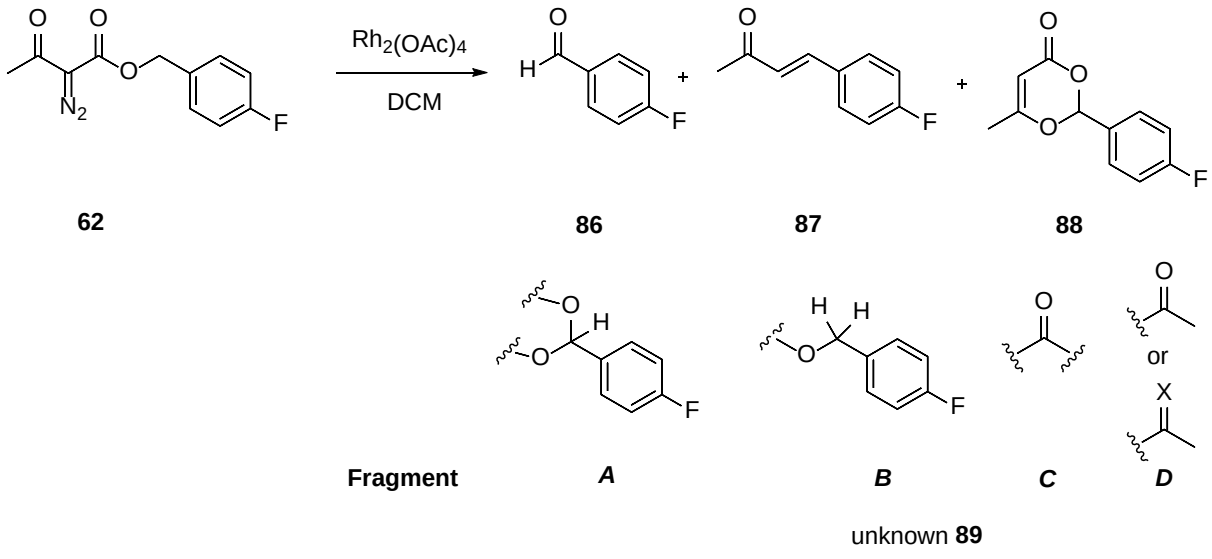
Entry	Loading (mol %)	Conditions	Time	Crude Product Ratio **82 : 83 : 84 : 85**
1	5	RT	18 h	1 : 2 : 0 : 0
2	5	Δ (40 °C)	1.5 h	10 : 5 : 1 : 0
3	0.04	MW (100 °C)	3 min	10 : 7 : 3 : 9

As can be seen above, 4-chlorobenzaldehyde **82** is the major product in all cases except the room temperature reaction. It is noteworthy that (*E*)-4-(4-chlorophenyl)but-3-en-2-one **83** is present in twice the amount as **82** for the room temperature reaction as apart from benzyl 2-diazo-3-oxobutanoate **zzx051**, all other derivatives have given the aldehyde as the major product under these conditions.

4.1.3.7 Decomposition of 4-fluorobenzyl 2-diazo-3-oxobutanoate **62**

As a comparison to the chloro derivative, 4-fluorobenzyl 2-diazo-3-oxobutanoate **62** was subjected to rhodium(II) acetate under microwave irradiation. The ^{1}H NMR spectrum of the

crude reaction mixture showed evidence of (*E*)-4-(4-fluorophenyl)but-3-en-2-one **87**, 2-(4-fluorophenyl)-6-methyl-4H-1,3-dioxin-4-one **88** and 4-fluorobenzaldehyde **86** as well as a similar unidentified product **89** to that isolated for the chloro derivative above, as illustrated in **Scheme 4.9**.



	86	87	88	89
Ratio in ^{1}H NMR spectrum of crude mixture:	2:	4:	1:	10
Isolated yield:	not isolated	25%	8%	-[1]

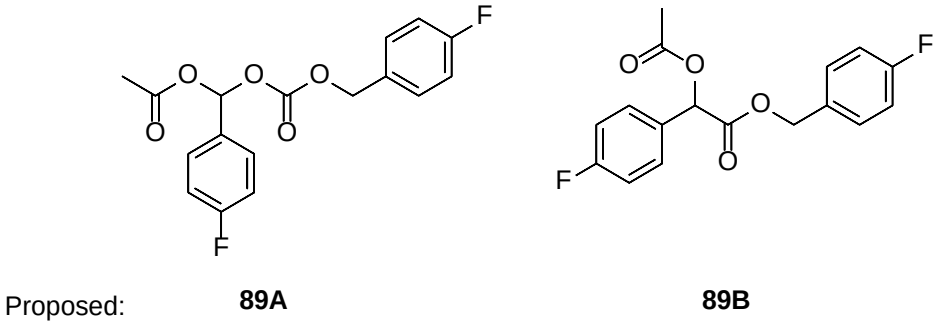
[1] 120 mg mass yield from 510 mg of **62**.

Scheme 4.9

Following column chromatography on silica gel, three fractions were isolated from the crude reaction mixture. The first contained an unknown compound **89**. The next fraction contained (*E*)-4-(4-fluorophenyl)but-3-en-2-one **87**, while the last fraction contained 2-(4-fluorophenyl)-6-methyl-4H-1,3-dioxin-4-one **88**. 4-fluorobenzaldehyde **86** could not be isolated although the ^{1}H NMR spectrum of several fractions had singlets at δ_H 10 ppm.

Unknown **89** was isolated as the major product from the above reaction mixture. As illustrated in **Scheme 4.9**, the same fragments are tentatively proposed for **89** as for **85** in **Section 4.1.3.6**. The spectra for both compounds are exceptionally similar, therefore it is proposed that they are analogous, differing only in the halide at the *para* position. Therefore

two structures are tentatively suggested for **89**, as shown in **Figure 4.10** below. As in the case of unknown **85** in **Section 4.1.3.6** above, both proposed structures, **89A** and **89B** differ only because **89A** has an ester group and a carbonate group, while **89B** has two ester groups. A similar NMR analysis was performed as was carried out for unknown **85**, and it was found that the NMR and IR data could potentially match either structure, however mass spectrometry has been indeterminate to date.

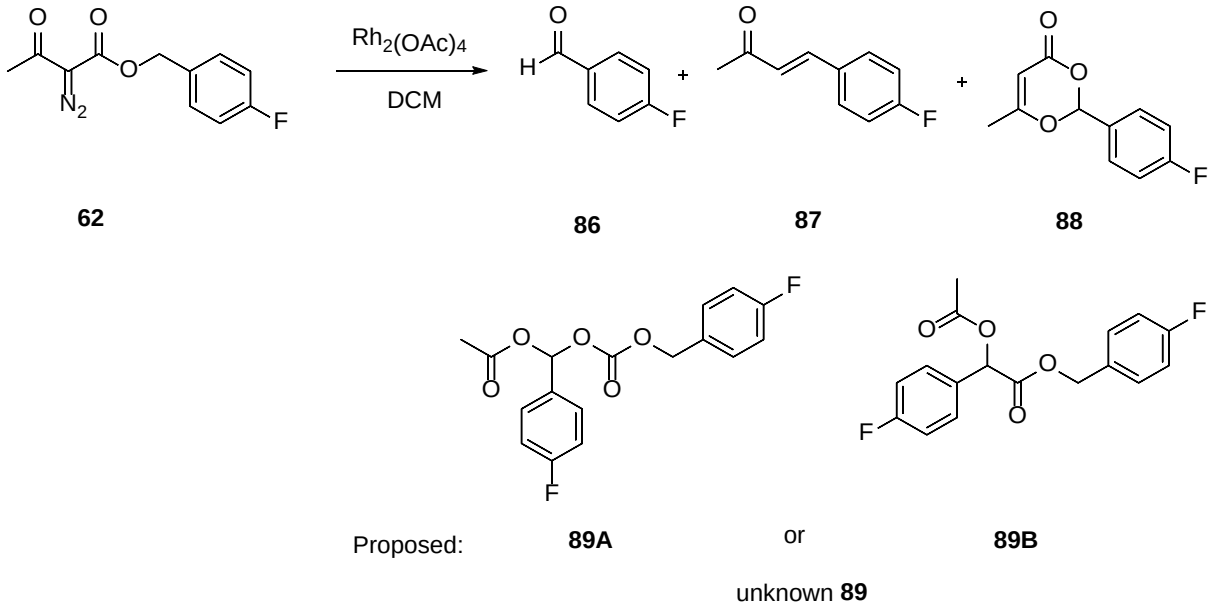


Proposed: **89A** **89B**

Figure 4.10 Tentatively proposed structures for **89**.

The results of subsequent decomposition experiments with 4-fluorobenzyl 2-diazo-3-oxobutanoate **62** are summarised in **Table 4.9**. As can be seen below, unknown **89**, although the major product from the decomposition reaction carried out in the microwave, was not observed in the ^{1}H NMR spectra of the room temperature or reflux decomposition reactions. Interestingly, for the first time evidence for the dioxinone product was observed when the crude reaction mixture of the room temperature reaction was analysed, although **88** was only isolated from the microwave decomposition mixture.

Table 4.9 ***Decomposition of 62 using $Rh_2(OAc)_4$ in DCM***



Entry	$Rh_2(OAc)_4$ Loading (mol %)	Conditions	Time	Crude Product Ratio 86 : 87 : 88 : 89
1	5	RT	18 h	12 : 10 : 1 : 0
2	5	Δ (40 °C)	1.5 h	10 : 10 : 1 : 0
3	0.04	MW (100 °C)	3 min	2 : 4 : 1 : 10

4.1.3.8 Decomposition of 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65**

As discussed in **Section 4.1.3.2**, two α-diazo-β-ketoesters were chosen for inclusion in these decomposition reactions in order to test the theory that the dioxinone products are being formed *via* formation of a stabilised carbocation intermediate. 4-(Trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65** has a strongly electron withdrawing triflate group which could destabilise any carbocation formed at this alpha position, as illustrated in **Figure 4.11**.

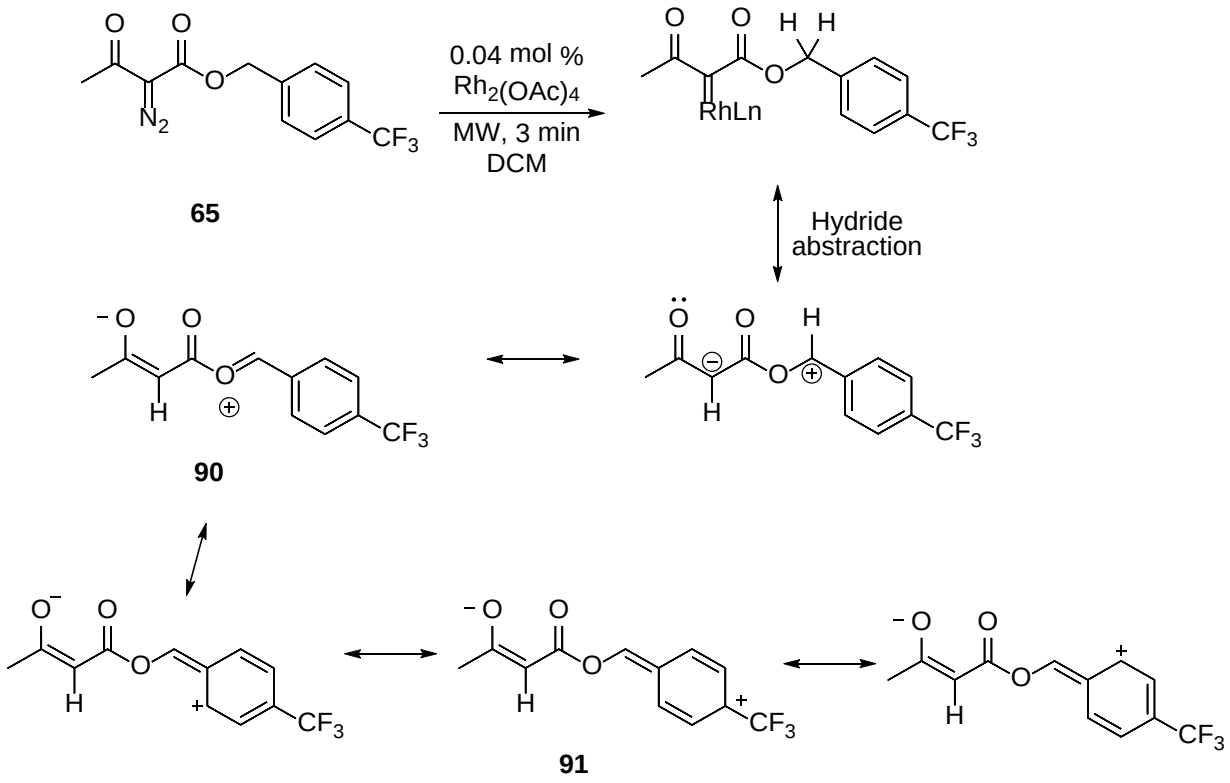
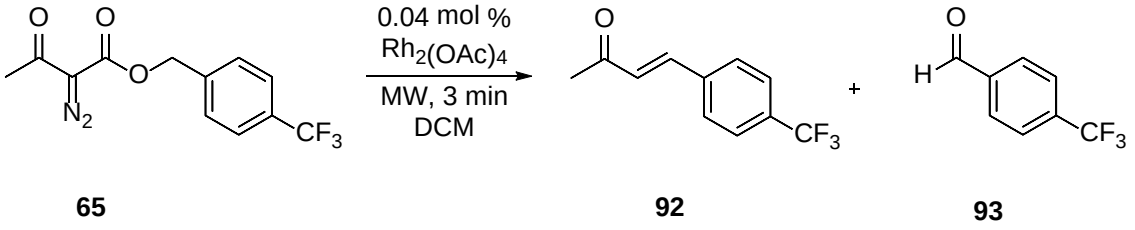


Figure 4.11 Resonance structures for delocalisation of cation around aromatic ring of **65**.

4-(Trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65** was reacted in the presence of rhodium(II) acetate under microwave conditions at 100 °C in dichloromethane for 3 mins, as for previous substrates (**Scheme 4.10**).



Ratio in ^{1}H NMR spectrum of crude mixture:	3	:	2
Isolated Yield:	Not isolated		Not isolated

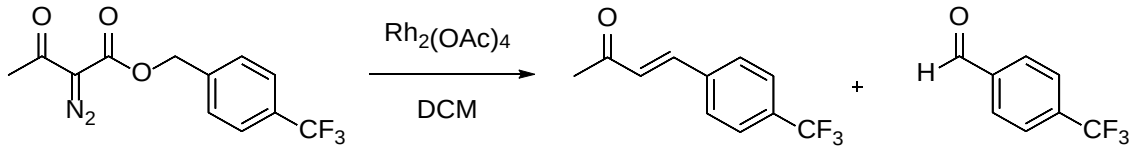
Scheme 4.10

When the ^{1}H NMR spectrum of the crude reaction mixture was examined, no evidence for the dioxinone product was observed. Therefore, the reaction was repeated under more forcing conditions, with 5 mol% rhodium(II) acetate for 10 minutes in the microwave. Again, no evidence for dioxinone formation was observed. The impact of these observations in terms of reaction pathway is dicussed in **Section 4.1.4**.

Evidence for the presence of 4-(4-(trifluoromethyl)phenyl)but-3-en-2-one **92** and 4-(trifluoromethyl)benzaldehyde **93** were observed in the ^{1}H NMR spectrum of the crude reaction mixture by their characteristic peaks at δ_H 6.69 ppm and δ_H 10.01 ppm respectively. Following column chromatography of the initial microwave reaction mixture, only fractions containing unidentifiable products were collected.

Room temperature and reflux decomposition reactions were also carried out with 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65**, the results of which are shown in **Table 4.10**. No evidence of dioxinone formation was seen under any reaction conditions, and although evidence for **92** and **93** was observed in each case in the ^{1}H NMR spectra of the crude reaction mixtures, the products were not isolated from any of these reaction mixtures. It is interesting to note that under room temperature and reflux conditions, 4-(trifluoromethyl)benzaldehyde **93** was seen to be the major product, however under microwave irradiation the opposite is seen with 4-(4-(trifluoromethyl)phenyl)but-3-en-2-one **92** present in a greater quantity.

Table 4.10 ***Decomposition of 65 using $Rh_2(OAc)_4$ in DCM***



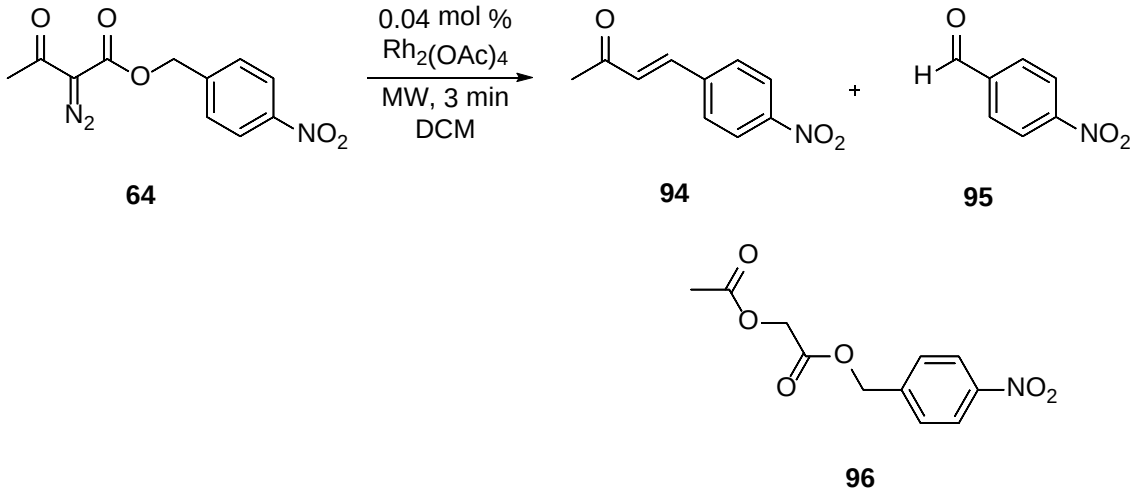
65 **92** **93**

Entry	$Rh_2(OAc)_4$ Loading (mol %)	Conditions	Time	Crude Product Ratio 92 : 93
1	5	RT	18 h	0 : 1
2	5	Δ (40 °C)	1.5 h	1 : 10
3	0.04	MW (100 °C)	3 min	3 : 2
4	5	MW (100 °C)	10 min	0 : 1

It is interesting to note here that in Entries 1,2 and 4 above 4-(trifluoromethyl)benzaldehyde **93** was the major product in the ^{1}H NMR spectra. However under the reaction conditions outlined in Entry 3, 4-(4-(trifluoromethyl)phenyl)but-3-en-2-one **92** is seen to be the major product. Benzyl 2-diazo-3-oxobutanoate **46** and 4-methylbenzyl 2-diazo-3-oxobutanoate **59** are the only other substrates which resulted in formation of the alkene as the major product under microwave irradiation.

4.1.3.9 Decomposition of 4-nitrobenzyl 2-diazo-3-oxobutanoate **64**

4-Nitrobenzyl 2-diazo-3-oxobutanoate **64** has similar electronic properties to 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65**, with a strongly electron withdrawing group on the aryl ring. **64** was reacted with rhodium(II) acetate under microwave conditions at 100 °C in dichloromethane for 3 mins, as shown in **Scheme 4.11** below.



64 **94** **95**

96

	zzx147		**zzx148**		**zzx149**
Ratio in ^{1}H NMR spectrum of crude mixture:	3	:	1	:	1
Isolated Yield:	Not isolated		Not isolated		10%

Scheme 4.11

As can be seen in **Scheme 4.11**, when the decomposition of 4-nitrobenzyl 2-diazo-3-oxobutanoate **64** was carried out under microwave conditions, an unexpected product was isolated from the crude reaction mixture. The product has been identified as 4-nitrobenzyl 2-acetoxyacetate **96** by NMR and mass spectrometry, as shown below in **Figure 4.12**. The mechanism of formation of **96** is not yet understood, however half of the molecule is likely from the ester side chain of the diazo starting material **64**.

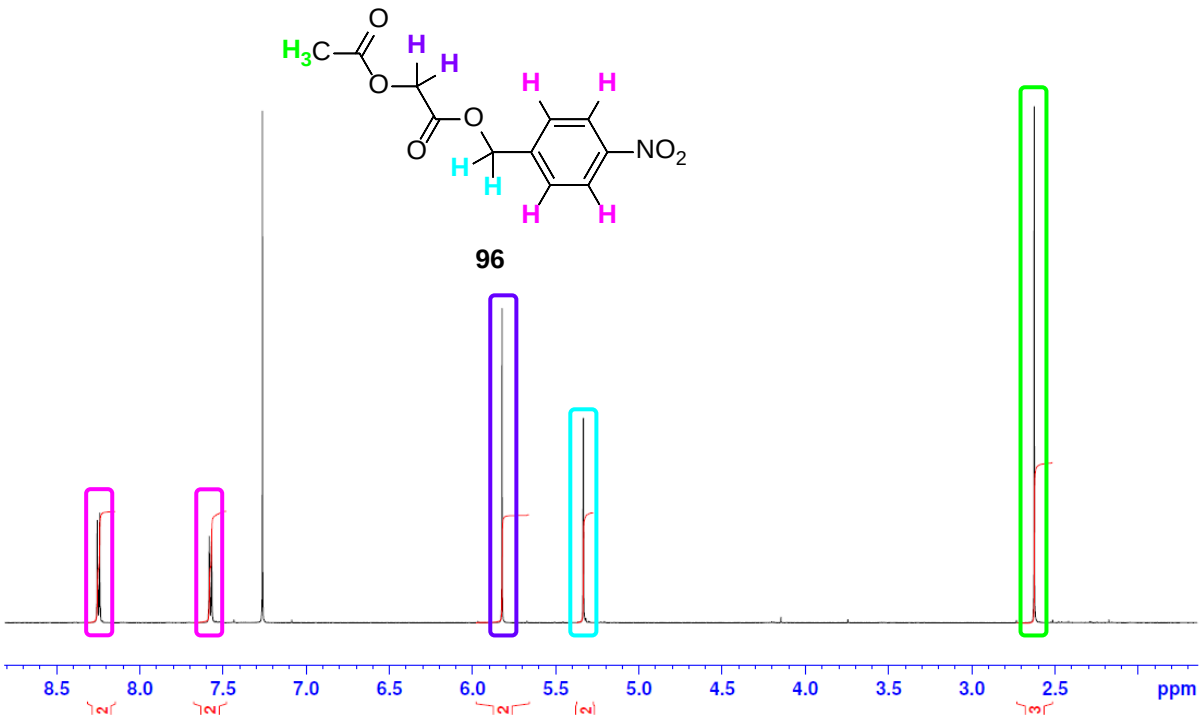
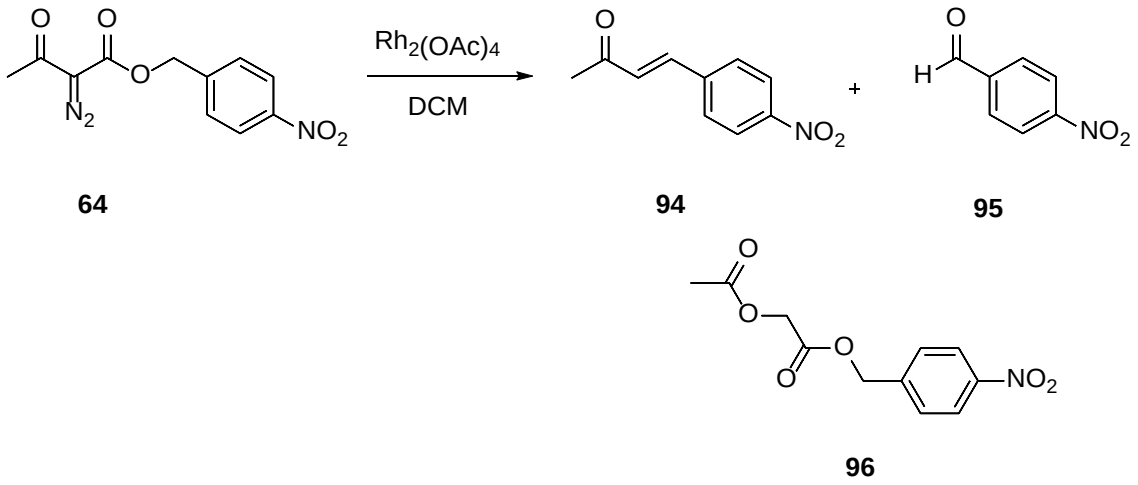


Figure 4.12 ^{1}H NMR spectrum of 4-nitrobenzyl 2-acetoxyacetate **96.**

Evidence for the presence of (*E*)-4-(4-nitrophenyl)but-3-en-2-one **94** and 4-nitrobenzaldehyde **95** was observed in the ^{1}H NMR spectrum of the crude reaction mixture by the characteristic peaks at δ_H 6.71 ppm and δ_H 9.91 ppm respectively, however neither were isolated following column chromatography. When the above reaction was carried out at room temperature and reflux, a different distribution of products was observed in the ^{1}H NMR spectra of the crude reaction mixtures, as outlined in **Table 4.11** below.

Table 4.11 below shows that although (*E*)-4-(4-nitrophenyl)but-3-en-2-one **94** is the major product in the crude reaction mixture when the above reaction is carried out under microwave irradiation, 4-nitrobenzyl 2-diazo-3-oxobutanoate **64** was observed to be the major product when the reaction was carried out at reflux.

Table 4.11 ***Decomposition of 64 using $Rh_2(OAc)_4$ in DCM***



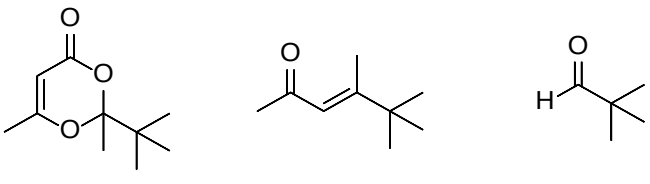
64 **94** **95** **96**

Entry	$Rh_2(OAc)_4$ Loading (mol %)	Conditions	Time	Crude Product Ratio 94 : 95 : 96
1	5	RT	18 h	2 : 1 : *
2	5	Δ (40 °C)	1.5 h	2 : 1 : 5
3	0.04	MW (100 °C)	3 min	3 : 1 : 1

* Unable to distinguish ratio due to signals of other decomposition products in same area of ^{1}H NMR spectrum.

4.1.3.10 Decomposition of 3,3-dimethylbutan-2-yl 3-oxobutanoate **57**

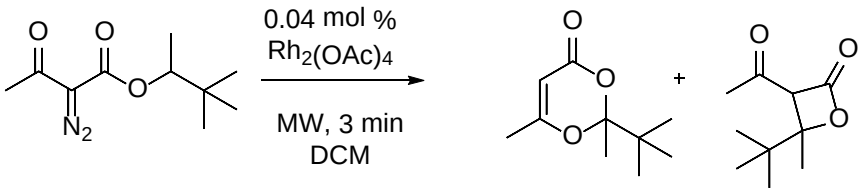
The first alkyl derivative to be decomposed under rhodium(II) catalysis in the course of this research was 3,3-dimethylbutan-2-yl 3-oxobutanoate **57**. If this substrate were to react in the same way as the benzyl diazo compounds previously used, the products to be expected are shown in **Figure 4.13**.



97 **98** **99**

Figure 4.13

Following decomposition of **57** under microwave irradiation in the presence of rhodium(II) acetate, the ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture of products, as shown below in spectrum (a) in **Figure 4.14**. Following column chromatography, two fractions of interest were isolated (**Scheme 4.13**).



57 **97** **100**

Ratio in ^{1}H NMR spectrum of crude mixture:	4	:	1
Isolated Yield:	16%		Not isolated

Scheme 4.13

The first, shown in spectrum (b) below, contained 3-acetyl-4-(tert-butyl)-4-methyloxetan-2-one **100** with other decomposition products. Disappointingly when this fraction was re-columned on silica gel to isolate **100**, the compound decomposed. This is the first case where evidence of the presence of the β-lactone was observed.

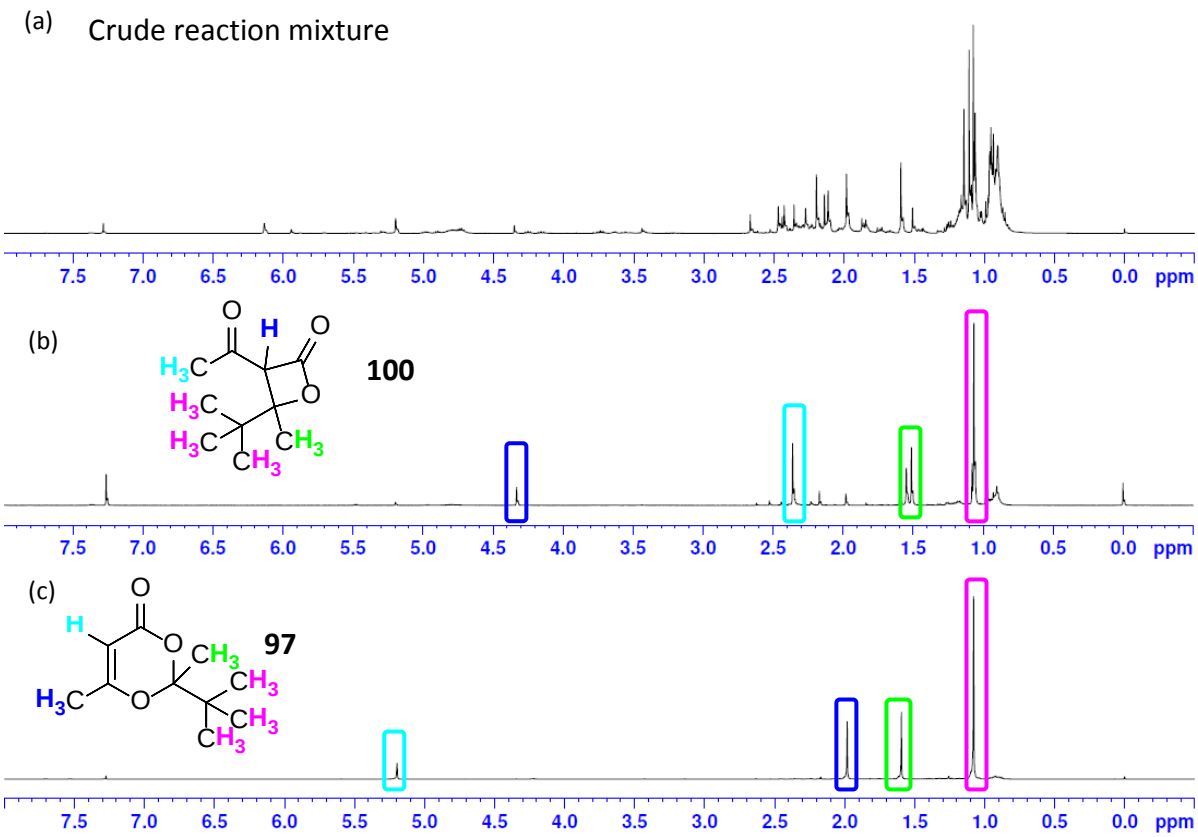


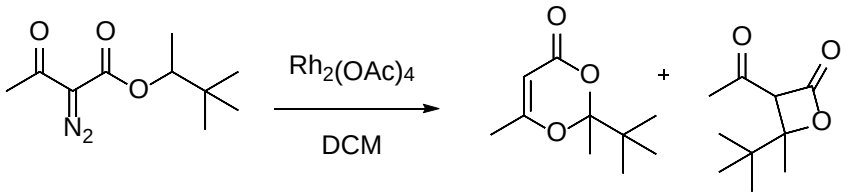
Figure 4.14 (a) ^{1}H NMR spectrum of crude reaction mixture from decomposition of **57** under microwave conditions, (b) ^{1}H NMR spectrum of fraction containing **100**, (c) ^{1}H NMR spectrum of 2-(tert-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **97.**

The second fraction isolated from the above reaction mixture contained 2-(tert-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **97**, the ^{1}H NMR of which is shown above in spectrum (c), **Figure 4.14**. **97** was isolated in only 16% yield, which is explained by the presence of several other unidentifiable decomposition products in the reaction mixture. This alkyl dioxinone has a distinctive 1H singlet at δ_H 5.19 ppm, which can be used to indicate its presence in the ^{1}H NMR spectrum of a crude reaction mixture.

Reflux and room temperature decomposition reactions were also done with 3,3-dimethylbutan-2-yl 3-oxobutanoate **57**. **Table 4.12** summarises the results of these reactions, and as can be seen below, **97** is only seen in the case of decomposition under microwave conditions. Decomposition of **57** under reflux conditions resulted in formation of 3-acetyl-4-

(tert-butyl)-4-methyloxetan-2-one **100**, while room temperature decomposition yielded neither product.

Table 4.12 ***Decomposition of 57 using $Rh_2(OAc)_4$ in DCM***



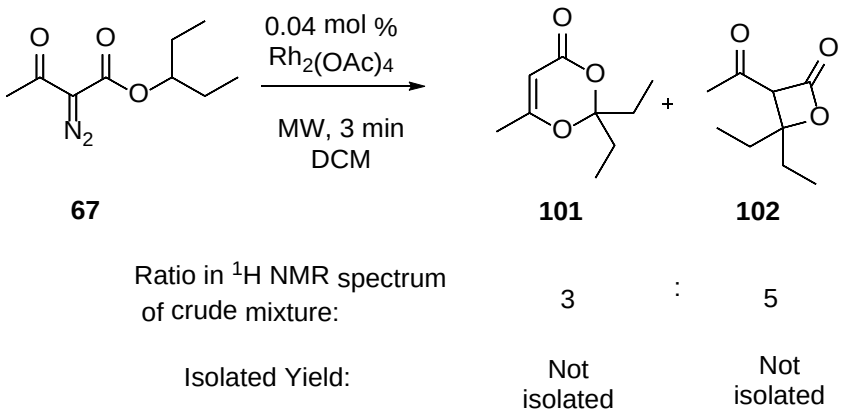
57 **97** **100**

Entry	$Rh_2(OAc)_4$ Loading (mol %)	Conditions	Time	Crude Product Ratio 97 : 100
1	5	RT	18 h	0 : 0
2	5	Δ (40 °C)	1.5 h	0 : 1
3	0.04	MW (100 °C)	3 min	4 : 1

As can be seen above, 2-(tert-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **97** was the major product of the reaction carried out under microwave irradiation, yet only 3-acetyl-4-(tert-butyl)-4-methyloxetan-2-one **100** was formed under reflux conditions.

4.1.3.11 Decomposition of pentan-3-yl 2-diazo-3-oxobutanoate **67**

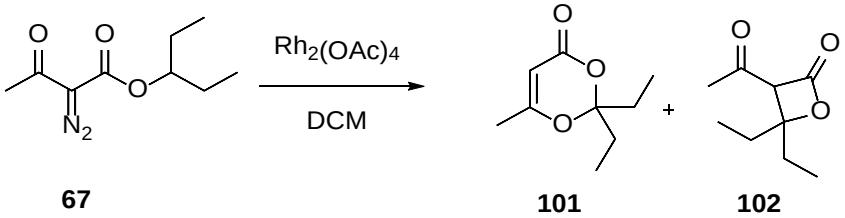
Pentan-3-yl 2-diazo-3-oxobutanoate **67** was the next alkyl derivative subjected to rhodium decomposition. The reaction was carried out under microwave irradiation at 100 °C for 3 minutes, as illustrated in **Scheme 4.14**. The ^{1}H NMR spectrum the crude reaction mixture showed evidence of both 2,2-diethyl-6-methyl-4H-1,3-dioxin-4-one **101** and 3-acetyl-4,4-diethyloxetan-2-one **102**, with 1H singlets at δ_H 5.19 ppm and δ_H 4.21 ppm respectively. Isolation of **101** and **102** from the crude reaction mixture proved unsuccessful despite repeated column chromatography.



Scheme 4.14

When further investigations were carried out into the reactivity of **67** in the presence of rhodium(II) acetate under reflux and room temperature conditions (**Table 4.13**), it was observed that β-lactone formation was the major pathway under reflux conditions. Unfortunately, no evidence of either **101** or **102** were observed when the reaction was done at room temperature.

Table 4.13 ***Decomposition of 67 using $Rh_2(OAc)_4$ in DCM***



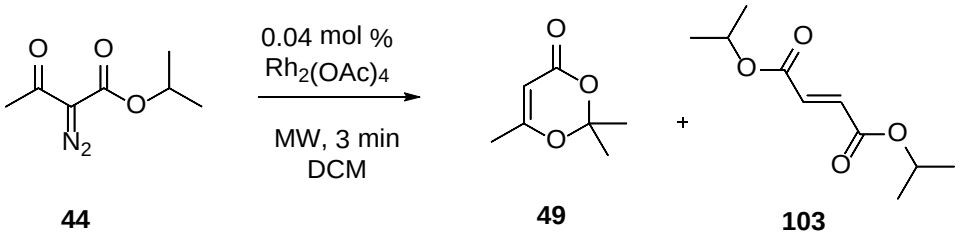
Entry	$Rh_2(OAc)_4$ Loading (mol %)	Conditions	Time	Crude Product Ratio 101 : 102
1	5	RT	18 h	0 : 0
2	5	Δ (40 °C)	1.5 h	0 : 1
3	0.04	MW (100 °C)	3 min	3 : 5

Although 3-acetyl-4,4-diethyloxetan-2-one **102** is the major product of both the reflux and microwave reactions, it could not be isolated from the crude reaction mixtures despite

repeated column chromatography. This is the only alkyl ester from this reaction series which gave β-lactone as the major product from microwave irradiation decompositions, as both **57** and **44** had dioxinone as the major decomposition product under these conditions.

4.1.3.12 Decomposition of isopropyl 2-diazo-3-oxobutanoate **44**

When isopropyl 2-diazo-3-oxobutanoate **44** was reacted with rhodium(II) acetate under microwave conditions, evidence was seen in the ^{1}H NMR spectrum of the crude reaction mixture for the presence of 2-(*t*-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **49** as illustrated in **Scheme 4.15**. This was indicated by the appearance of a signal at δ_H 5.25 ppm. Following column chromatography on silica gel, **49** was isolated in 16% yield.

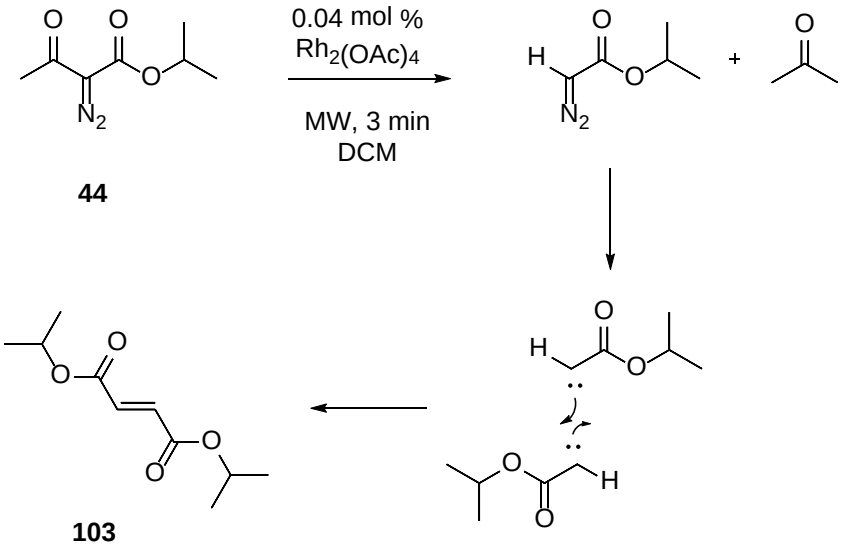


Ratio in ^{1}H NMR spectrum of crude mixture:	2	:	3
Isolated Yield:	16%		30%

Scheme 4.15

When the decomposition of isopropyl 2-diazo-3-oxobutanoate **44** was carried out under microwave conditions, an unexpected side product was isolated from the crude reaction mixture. The product has been identified as diisopropyl maleate **103** by NMR and mass spectrometry, which are in agreement with the literature values[4]. IR spectroscopy was used to tentatively assign the double bond geometry as *trans*, with a strong absorption at 947 cm^{-1}.

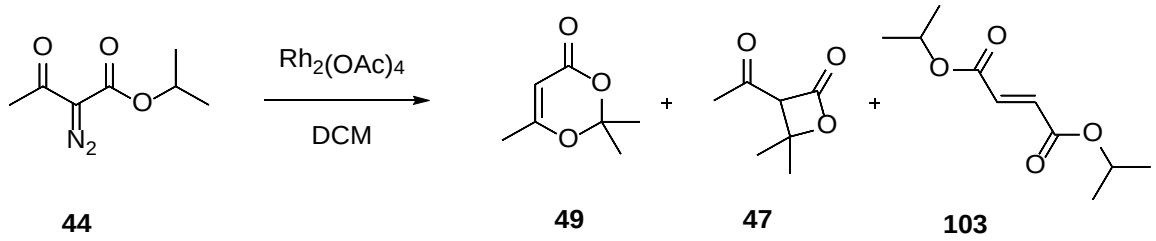
Hendrickson and Wolff reported hydrolysis of α-diazocarbonyl compounds, as shown for **44** in **Scheme 4.16** below.[5] **103** may possibly be formed by dimerization of the carbene generated from the hydrolysis product of **44**.



Scheme 4.16

While no evidence for the presence of 3-acetyl-4,4-dimethyloxetan-2-one **47** was observed in the reaction mixture described above, it was found to be the major product in the ^{1}H NMR spectra of the crude reaction mixtures of the room temperature and reflux decomposition reactions, as outlined in **Table 4.14** below.

Table 4.14 ***Decomposition of 44 using $Rh_2(OAc)_4$ in DCM***



44 **49** **47** **103**

Entry	$Rh_2(OAc)_4$ Loading (mol %)	Conditions	Time	Crude Product Ratio 49 : 47 : 103
1	5	RT	18 h	0 : 1 : 0
2	5	Δ (40 °C)	1.5 h	1 : 8 : *
3	0.04	MW (100 °C)	3 min	2 : 0 : 3

* Unable to distinguish ratio due to signals of other decomposition products in same area of ^{1}H NMR spectrum.

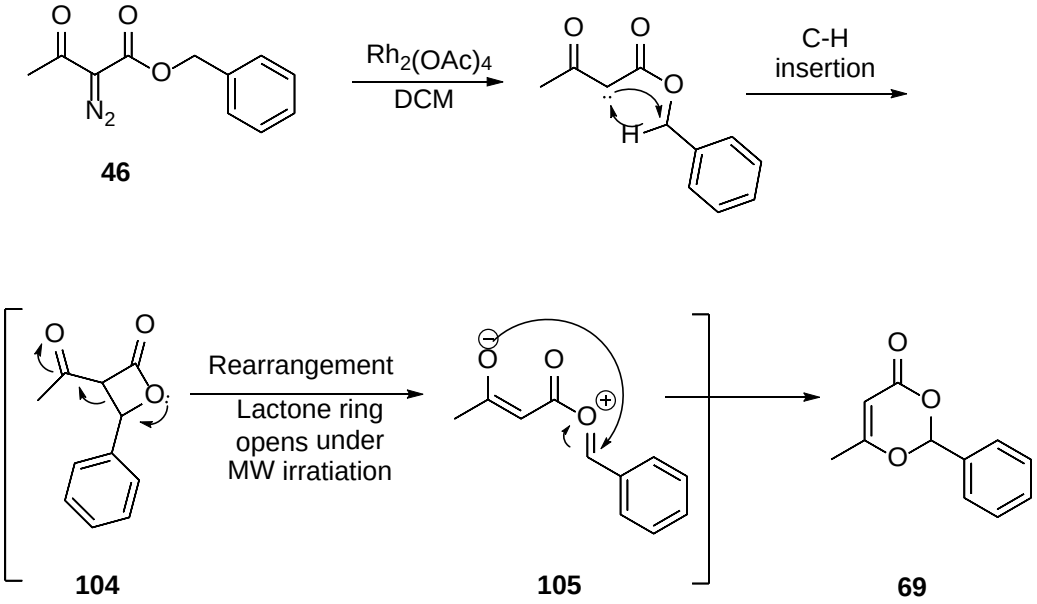
It is interesting to note that although 3-acetyl-4,4-dimethyloxetan-2-one **47** is the major product of the room temperature and reflux reactions it is not present in the ^{1}H NMR spectrum of the microwave reaction. Although evidence for diisopropyl maleate **103** was seen in the ^{1}H NMR spectrum of the reflux reaction mixture, it was not isolated following column chromatography.

4.1.4 Mechanistic insight into product formation

As discussed above in **Section 4.1.1**, based on the structural features of the α-diazo-β-ketoester compounds which gave dioxinone products following decomposition in the presence of rhodium(II) acetate, it was proposed that a stabilised carbocation is a key intermediate in the formation of dioxinones from α-diazocarbonyl compounds.

A proposed mechanism for the formation of **69** *via* C-H insertion is outlined in **Scheme 4.17**. The suggested mechanism proceeds *via* loss of N_2 from **46** to generate the carbene, followed by C-H insertion to form the β-lactone **104** which could then ring open *via* nucleophilic attack from the lone pair of electrons on the lactone oxygen leading to the intermediate **105** shown

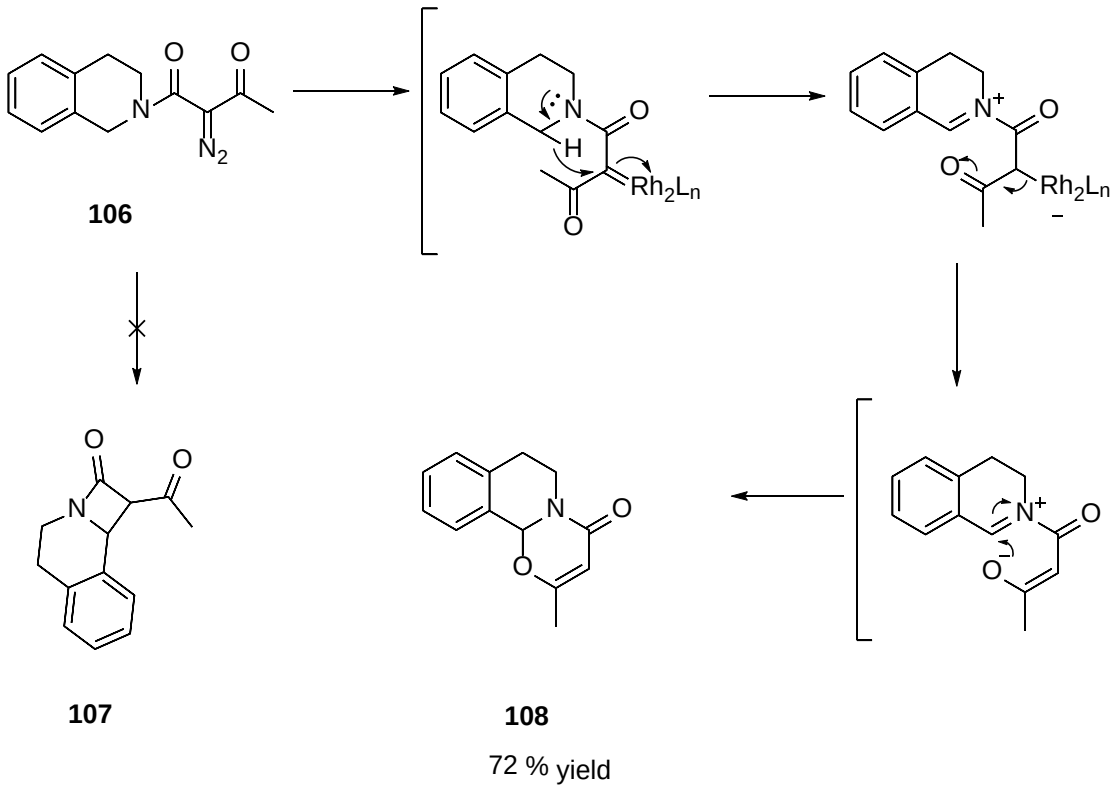
below. We propose that the carbocation intermediate would be stabilised either by resonance electron donating groups or inductive effects, and therefore designed our α-diazo-β-ketoester precursors with this in mind. Subsequent rearrangement of the carbocation intermediate **105** results in the formation of **69**.



46 **104** **105** **69**

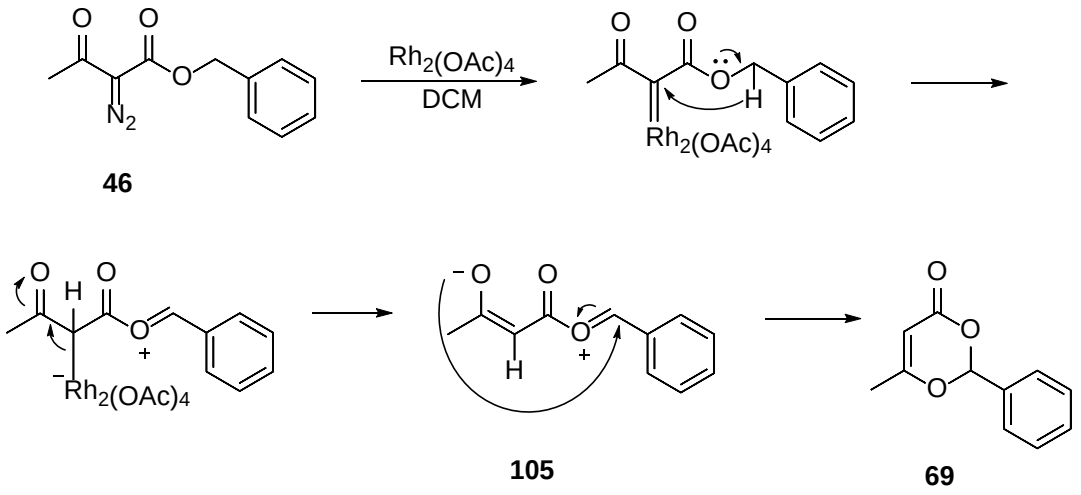
Scheme 4.17

Another possible reaction pathway by which the dioxinone may be formed is *via* intramolecular metal-carbene hydride-abstraction (hydride transfer), which has been reported as a competing pathway to C-H insertion in decomposition reactions of diazocarbonyl compounds.[6–9] Chelucci *et al*. reported formation of a 1,3-oxazin-4-one ring **108** rather than the expected β-lactam **107** from the rhodium catalysed decomposition of an isoquinoline diazoamide **106** (**Scheme 4.18**),[10] a pathway which is consistent with a hydride-transfer reaction pathway.



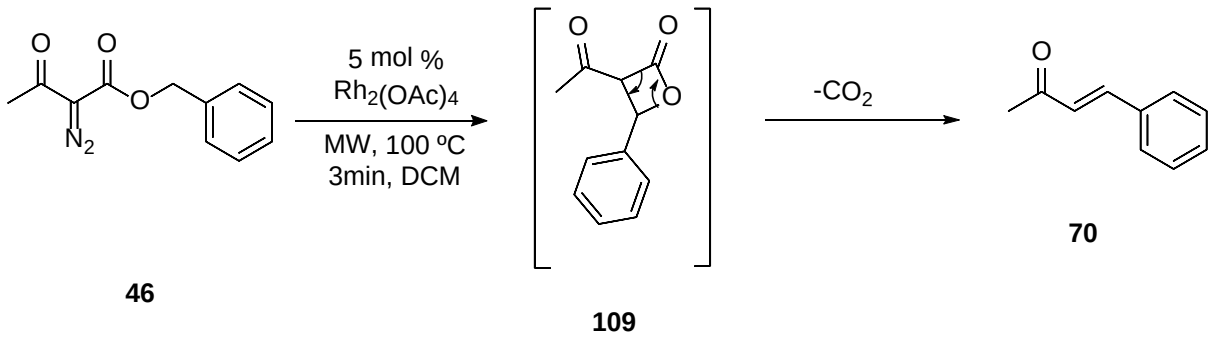
Scheme 4.18

The authors propose that **106** is formed *via* hydride migration to the carbenoid, giving rise to an intermediate which possesses an iminium ion and a rhodium enolate. Subsequent nucleophilic attack by the oxygen on the rhodium enolate on the highly reactive iminium ion results in the formation of the six membered ring product **106**. The theory behind this mechanism can also be applied to our α-diazo-β-ketoester substrates. This is illustrated for benzyl 2-diazo-3-oxobutanoate **46** in **Scheme 4.19** below. It should be noted that this mechanism proceeds *via* the same stabilised carbocation **105** described in **Scheme 4.17**.



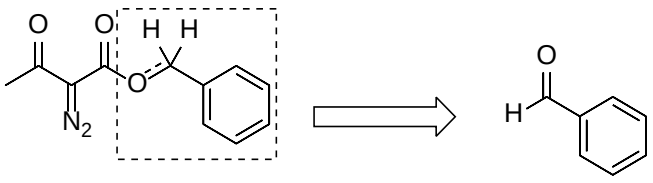
Scheme 4.19

As seen in **Section 4.1.3**, decarboxylation products such as (*E*)-4-phenylbut-3-en-2-one **70** were isolated from the decomposition reactions of nearly all benzyl diazo derivatives used. These are likely formed by decarboxylation of the corresponding β-lactone **109**, as illustrated in **Scheme 4.20**, supporting the mechanism suggested in **Scheme 4.17** above.



Scheme 4.20

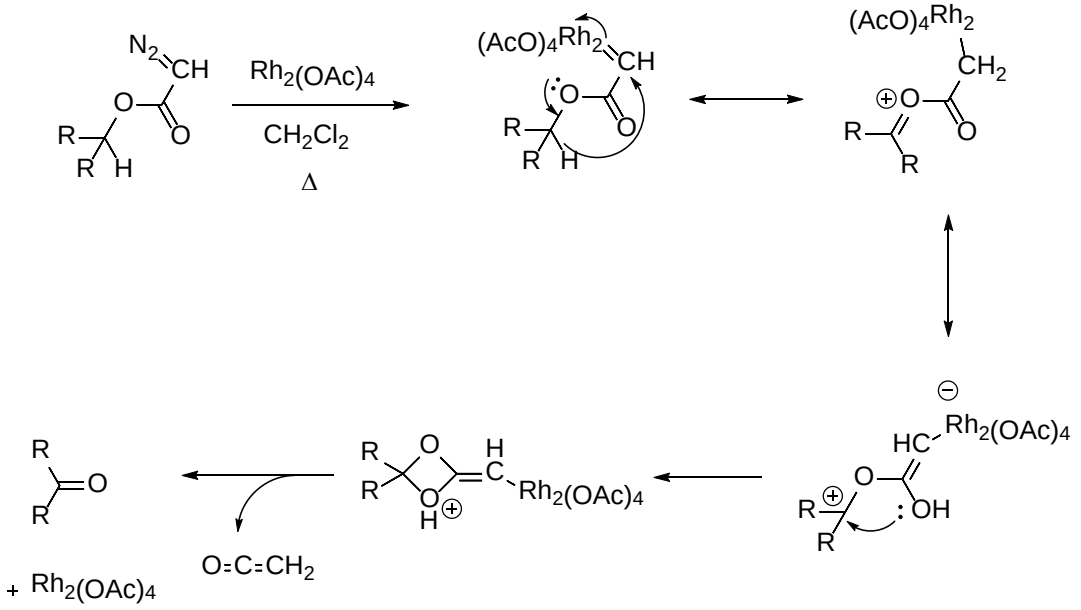
When trying to determine the mechanism by which the aldehyde products seen in **Section 4.1.3** are formed, the most apparent pathway appears to be by hydride abstraction also, as the ester side chain appears to be converted to the analogous aldehyde, as shown in **Figure 4.14**.



46 **71**

Figure 4.14

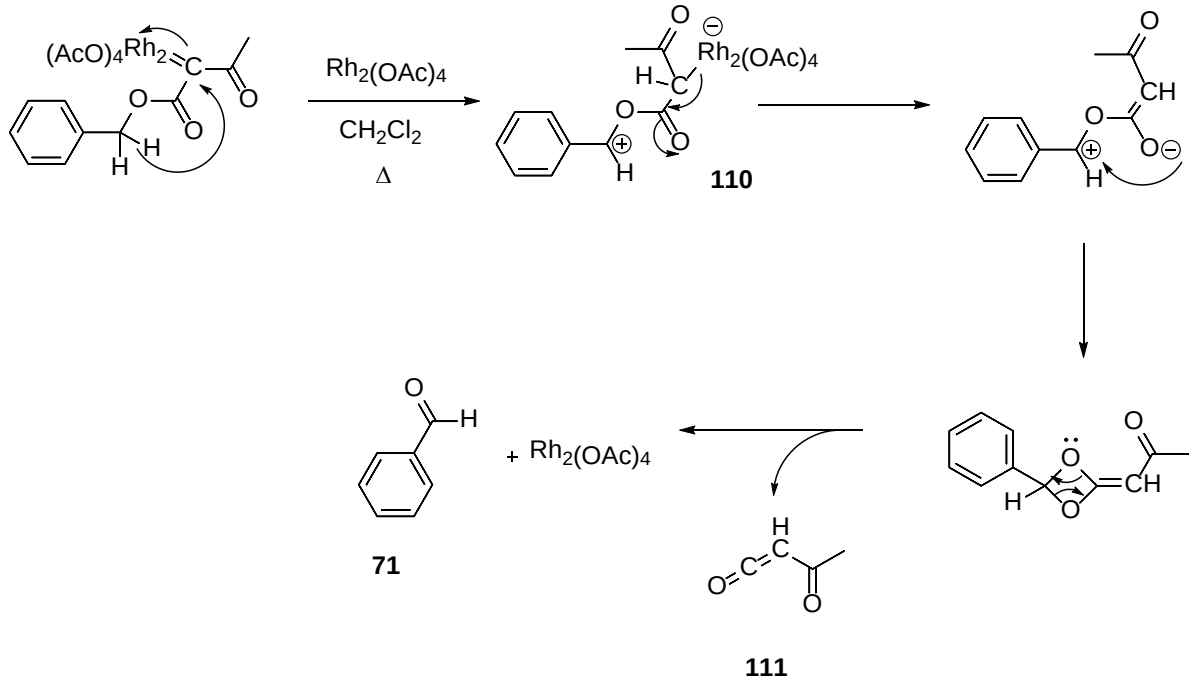
Doyle and co-workers reported hydride abstraction as a competing pathway to intermolecular C-H insertion to form β-lactones in the case of secondary benzylic and allylic diazoacetates (**Scheme 4.21**).[7]



Scheme 4.21

Application of this theory to the α-diazo-β-ketoesters used in this project offers a plausible mechanism for the formation of the series of aldehydes observed in the course of this research, as illustrated in **Scheme 4.22** for **46**. As can be seen below, hydride abstraction leads to a stabilised carbocation intermediate **110**, similar to that outlined in the proposed mechanism for dioxinone formation (**Scheme 4.17**). It is interesting that if this mechanism holds, then an enolate formed on the ketone side leads to formation of dioxinone (**Scheme**

4.17), while an enolate formed on the ester side leads to formation of the aldehyde (**Scheme 4.22**).



Scheme 4.22

However on further examination of the results obtained, a discrepancy was detected. If both the aldehyde and dioxinone were formed *via* a common intermediate, there should be a direct correlation between which substrates yielded each product. While many α-diazo-β-ketoesters gave both products following rhodium(II) catalysed decomposition, a number of diazo compounds yielded only aldehyde or dioxinone. Therefore it was necessary to compare all α-diazo-β-ketoesters used in the course of this research and the products that they yielded under various conditions. These results are summarised in **Tables 4.15- 4.17**, with the diazo compounds listed in order from most electron withdrawing substituents on top to most electron donating substituents towards the bottom. R in **Tables 4.15- 4.17** is defined as outlined in **Figure 4.15** below.

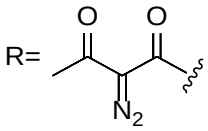
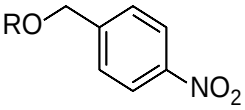
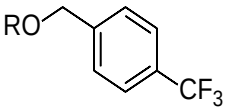
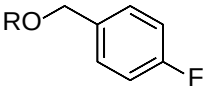
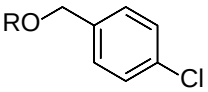
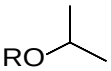
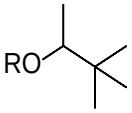
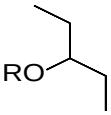
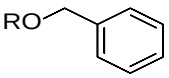
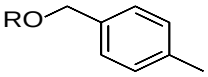
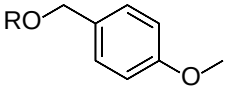
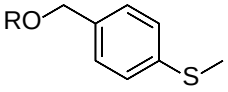


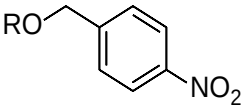
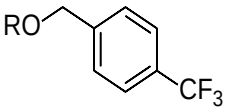
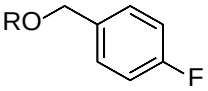
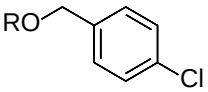
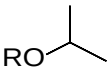
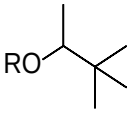
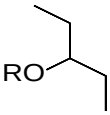
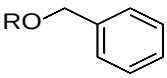
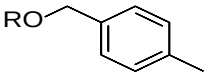
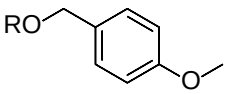
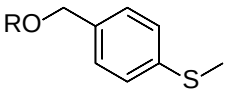
Figure 4.15

Table 4.15 Summary of results from microwave decompositions [0.04 mol% $Rh_2(OAc)_4$]

Entry	*R*		*Aldehyde*	*Dioxinone*	*Alkene*
1		Present:	✓	×	✓
		Ratio:	1:	0:	3
2		Present:	✓	×	✓
		Ratio:	2:	0:	3
3		Present:	✓	✓	✓
		Ratio:	2:	1:	4
4		Present:	✓	✓	✓
		Ratio:	10:	3:	7
5		Present:	×	✓	×
		Ratio:	0:	1:	0
6		Present:	×	✓	×
		Ratio:	0:	1:	0
7		Present:	×	✓	×
		Ratio:	0:	1:	0
8		Present:	✓	✓	✓
		Ratio:	1:	3:	5
9		Present:	✓	✓	✓
		Ratio:	2:	3:	3
10		Present:	✓	✓	✓
		Ratio:	5:	5:	1
11		Present:	✓	×	✓
		Ratio:	4:	0:	3

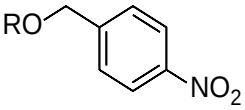
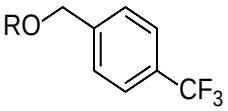
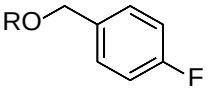
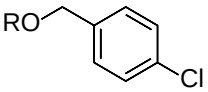
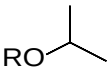
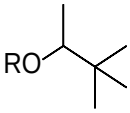
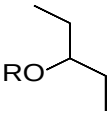
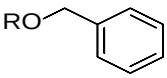
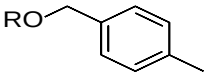
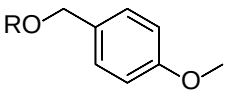
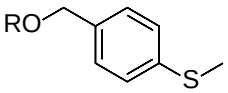
Presence/absence of product in the ^{1}H NMR spectrum of crude reaction mixture indicated by ✓/×. * indicates that each present in the ^{1}H NMR spectrum of the crude reaction mixture, but due to the presence of peaks corresponding to other decomposition products in the same region, a crude product ratio could not be obtained.

Table 4.16 Summary of results from reflux decompositions [5 mol% $Rh_2(OAc)_4$]

Entry	*Diazo Compound*		*Aldehyde*	*Dioxinone*	*Alkene*
1		Present:	✓	×	✓
		Ratio:	1:	0:	2
2		Present:	✓	×	✓
		Ratio:	10:	0:	1
3		Present:	✓	✓	✓
		Ratio:	10:	1:	10
4		Present:	✓	✓	✓
		Ratio:	10:	1:	5
5		Present:	×	✓	×
		Ratio:	0:	1:	0
6		Present:	×	✓	×
		Ratio:	0:	1:	0
7		Present:	×	✓	×
		Ratio:	0:	1:	0
8		Present:	✓	×	✓
		Ratio:	1:	0:	1
9		Present:	✓	✓	✓
		Ratio:	10:	3:	5
10		Present:	✓	✓	✓
		Ratio:	5:	2:	1
11		Present:	✓	×	✓
		Ratio:	4:	0	3

Presence/absence of product in the ^{1}H NMR spectrum of crude reaction mixture indicated by ✓/×. * indicates that each present in the ^{1}H NMR spectrum of the crude reaction mixture, but due to the presence of peaks corresponding to other decomposition products in the same region, a crude product ratio could not be obtained.

Table 4.17 Summary of results from room temperature decompositions [5 mol% $Rh_2(OAc)_4$)

Entry	*R*		*Aldehyde*	*Dioxinone*	*Alkene*
1		Present:	✓	×	✓
		Ratio:	1:	0:	2
2		Present:	✓	×	×
		Ratio:	1:	0:	0
3		Present:	✓	✓	✓
		Ratio:	12:	1:	10
4		Present:	✓	×	✓
		Ratio:	1:	0:	2
5		Present:	×	×	×
		Ratio:	0:	1:	0
6		Present:	×	✓	×
		Ratio:	0:	1:	0
7		Present:	×	✓	×
		Ratio:	0:	1:	0
8		Present:	✓	×	✓
		Ratio:	4:	0:	3
9		Present:	✓	×	✓
		Ratio:	2:	0:	1
10		Present:	✓	×	✓
		Ratio:	10:	0:	1
11		Present:	✓	×	✓
		Ratio:	2:	0:	1

Presence/absence of product in the ^{1}H NMR spectrum of crude reaction mixture indicated by ✓/×. * indicates that each present in the ^{1}H NMR spectrum of the crude reaction mixture, but due to the presence of peaks corresponding to other decomposition products in the same region, a crude product ratio could not be obtained.

Table 4.15 (MW conditions) shows that for the more electron donating substrates (Entries 5-10) the dioxinone is formed as one of the major products from reactions carried under microwave irradiation. Interestingly Entry 11 above shows that 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** is the exception to this. It is possible that the large amount of electron density from the very strongly electron donating sulfide group is actually causing the dioxinone to break down when it is formed.

For the more electron withdrawing groups (entries 1-4), the dioxinone is formed as the minor product when a fluoro or chloro group is in place in the molecule. However for strongly electron withdrawing groups like triflate or nitro, no evidence of dioxinone formation is seen.

Entries 5-7 in **Table 4.15** show the results of decomposition reactions with alkyl ester side chain derivatives. It is noteworthy that this class of diazo products yields no alkene or aldehyde products under any of the three conditions used. This has implications from a mechanistic perspective, which will be discussed later.

Entries 8-10 in **Table 4.15** show an interesting progression. As can be seen, when the entries from unsubstituted to increasingly strong electron donating substituents are examined, there is an increase in the relative quantity of aldehyde observed in the crude reaction mixture, while the relative quantity of alkene present decreases.

Table 4.16 (reflux conditions) has some similar results when compared to **Table 4.15**; neither the strong electron donating or electron withdrawing substituents yield dioxinone under these reaction conditions. In contrast, dioxinone is still the major product of the decomposition reactions of the alkyl derivatives, with no alkene or aldehyde products observed.

An interesting feature of the reactions outlined in **Table 4.16** is that the aldehyde is one of the major products for every benzyl derivative under these conditions. In contrast, the dioxinone product is present in relatively small amounts under these conditions when compared to **Table 4.15**.

Comparison of Entries 8-10 in **Table 4.16** (reflux conditions) highlights an unusual trend. As the strength of the electron donating substituent is increased from hydrogen to methoxy, there are significant changes in the proportion of various products. Entry 8 shows a 1:1 ratio

of aldehyde to alkene, with no dioxinone formed. When a methyl group is introduced at the *para* position, evidence for dioxinone formation is now observed, and the alkene and aldehyde are present in a ratio of 10:5 (or 2:1). Increasing the strength of the electron donating substituent further by introducing a methoxy group in Entry 10 alters the proportion of aldehyde to alkene to a 5:1 ratio, with no significant change to the quantity of dioxinone observed.

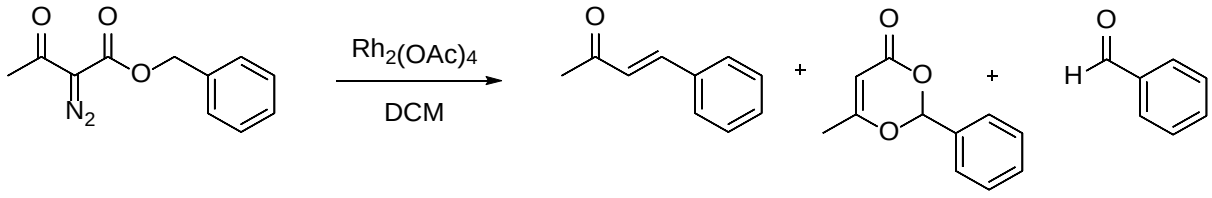
In **Table 4.17** (r.t. conditions) we can see that the aldehyde product is the major product of decomposition reactions carried out at room temperature for benzyl derivatives with electron donating substituents. For benzyl derivatives with electron donating substituents, the alkene product was generally observed to be the major product, except for in the case of **65**, as outlined in Entry 2.

It is interesting to note that apart from the alkyl derivatives, 4-fluorobenzyl 2-diazo-3-oxobutanoate **62** was the only substrate to yield dioxinone at room temperature (**Table 4.17**, Entry 3).

If all three tables are compared to each other, different trends can be observed. When the same reactions are carried out under reflux conditions as for microwave irradiation, the same pattern in formation of dioxinone is observed, in that derivatives with very strongly electron donating or electron withdrawing substituents do not yield dioxinone (**Table 4.16**). However for the electron donating groups, although the dioxinone is still formed, it is no longer formed as the major product of the reaction except in the case of the three alkyl diazo compounds. This trend is continued in **Table 4.15** which outlines reactions carried out at room temperature.

If we examine Entry 8 in **Tables 4.15- 4.17**, an interesting progression is observed. When the decomposition of benzyl 2-diazo-3-oxobutanoate **46** was carried out under microwave irradiation, five times as much alkene **70** was observed in comparison to the aldehyde **71** as summarised below in **Table 4.4** (extracted from pg. 255). When the same reaction is carried out under reflux conditions, no dioxinone **69** is observed in the crude reaction mixture, and the ratio of **70** to **71** is 1:1. This is ratio leans slightly in the favour of **70** when the reaction is done at room temperature, with a 3:3 ratio observed.

Table 4.4 ***Decomposition of 46 using $Rh_2(OAc)_4$ in DCM*** **(from pg. 255)**

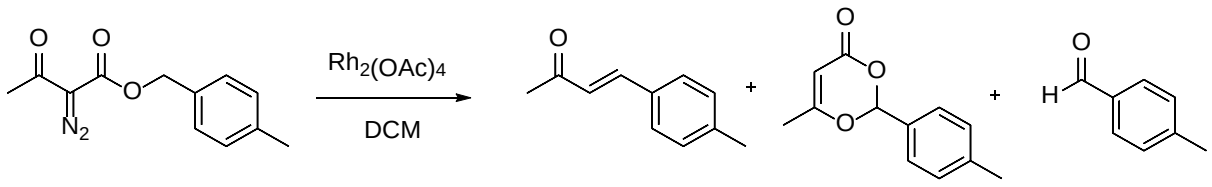


46 **70** **69** **71**

Entry	$Rh_2(OAc)_4$ Loading (mol%)	Conditions	Time	Crude Product Ratio 70 : 69 : 71
1	5	RT	18 h	4 : 0 : 3
2	5	Δ (40 °C)	1.5 h	1 : 0 : 1
3	0.04	MW (100 °C)	3 min	5 : 3 : 1

Examining all three tables together, another pattern is observed: as the amount of dioxinone in the reaction mixture decreases, the relative amount of aldehyde increases, as illustrated in **Table 4.5** below (extracted from pg. 257).

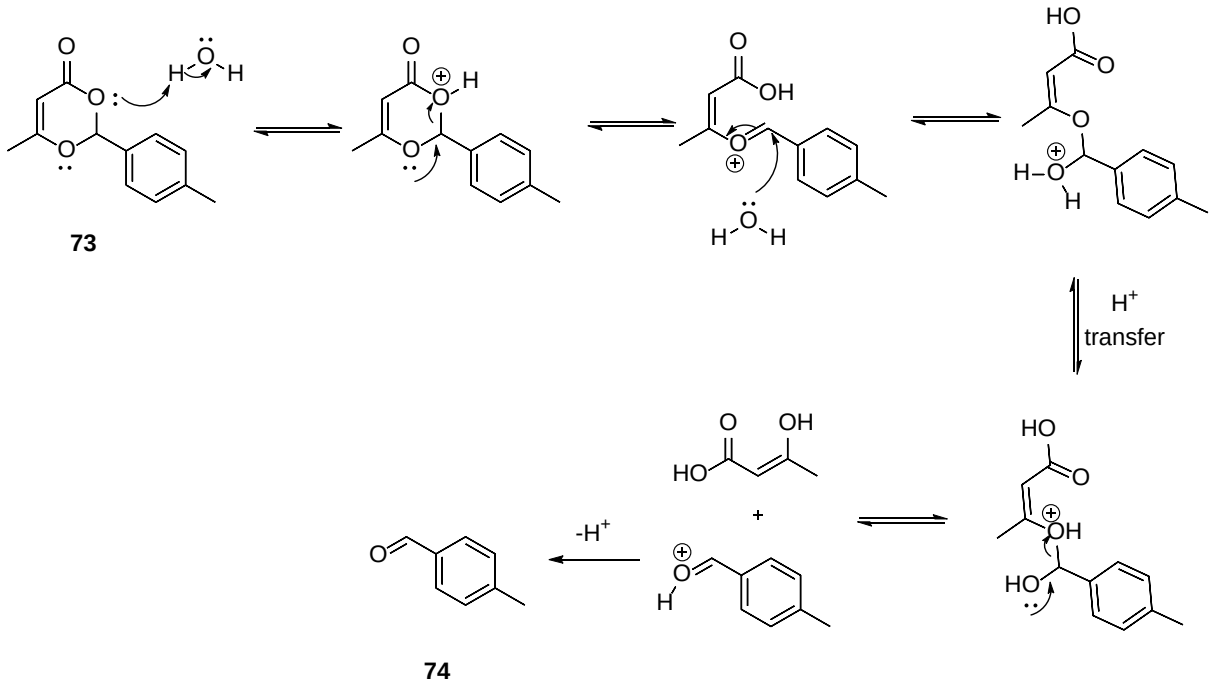
Table 4.5 ***Decomposition of 59 using $Rh_2(OAc)_4$ in DCM (from pg. 257)***



59 **72** **73** **74**

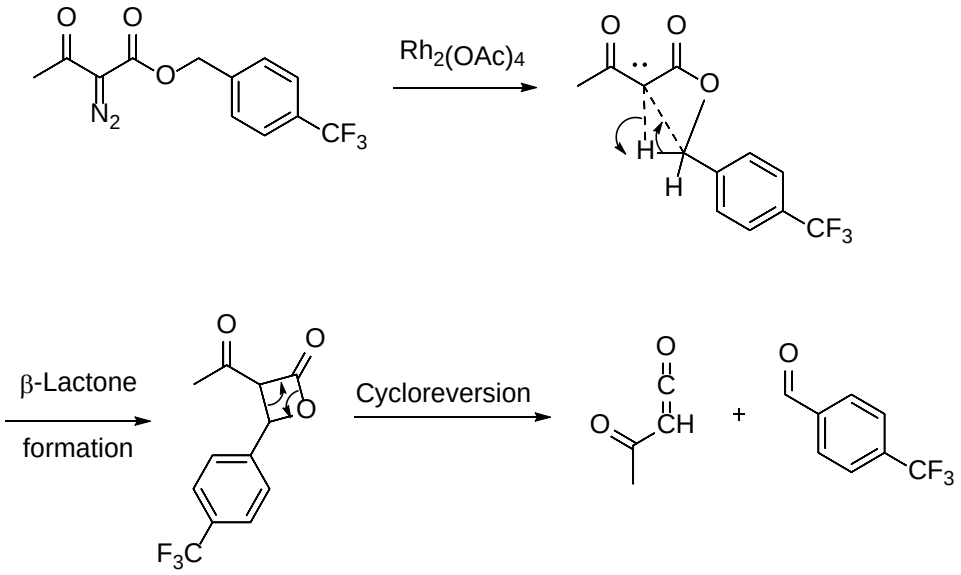
Entry	$Rh_2(OAc)_4$ Loading (mol%)	Conditions	Time	Crude Product Ratio 72 : 73 : 74
1	5	RT	18 h	1 : 0 : 2
2	5	Δ (40 °C)	1.5 h	5 : 3 : 10
3	0.04	MW (100 °C)	3 min	3 : 3 : 2

As can be seen above, although the relative amount of dioxinone present in the reaction mixture is unchanged, the relative quantity of aldehyde has increased fivefold. This might suggest that dioxinone is in fact forming in large quantities under both reflux and room temperature conditions, but with the significantly longer reaction times the dioxinone is then decomposing to the aldehyde in the presence of adventitious water similar to an acetal hydrolysis, as illustrated in **Scheme 4.23**.



Scheme 4.23

It is probable that aldehyde derivatives are being formed *via* more than one mechanistic pathway. As mentioned above, dioxinones are not observed as products when very electron withdrawing groups, such as triflate and nitro are part of the α-diazo-β-ketoester, yet these substrates still yield aldehyde products. Therefore aldehydes are likely to be formed either *via* the route proposed by Doyle as outlined above (**Scheme 4.20**), or by another route which does not involve a stabilised carbocation intermediate. This may be achieved by a cycloreversion mechanism following C-H insertion of the carbene as outlined in **Scheme 4.24**.



Scheme 4.24

Scheme 4.20 (pg. 287) outlines the mechanism of formation of the alkene products observed for all benzyl derivatives *via* decarboxylation of the β-lactone product. The fact that alkene formation is observed, sometimes even as the major reaction product, for both electron withdrawing and electron donating substituents lends weight to the proposed mechanism outlined in **Scheme 4.24** and in **Scheme 4.17** (pg. 285) above, as all three mechanisms proceed through the β-lactone intermediate, suggesting C-H insertion is the major reaction pathway.

It should be noted that although the three alkyl α-diazo-β-ketoester derivatives used in these decomposition reactions did not show evidence of formation of either aldehyde or alkene, there was evidence of β-lactone in the ^{1}H NMR spectra of many reaction mixtures. This strengthens the theory that C-H insertion is the major pathway, and seems to suggest that these alkyl derivatives yield more stable dioxinones, which are not susceptible to further rearrangement or decomposition.

Overall, to synthesise alkenes of the type isolated in this research, the best conditions to use would be with an electron withdrawing substituent on the benzyl side chain using microwave irradiation in the presence of rhodium(II) acetate. The presence of the electron withdrawing group suppresses the competitive formation of dioxinone, and carrying out these reactions

under microwave conditions has led to the greatest quantity of alkene in the crude reaction mixtures.

In contrast, if dioxinone was the desired reaction product, presence of inductive or resonance electron donating groups would promote the formation of this product. Alkyl ester side chains particularly favour formation of dioxinone products as the only other products formed in their decomposition reactions are β-lactones. Carrying out the decomposition under microwave irradiation has been observed to give the largest quantity of dioxinone product for all derivatives.

Aldehydes may be preferentially synthesised with this method by carrying out decomposition at room temperature. The mild conditions and longer reaction times led to formation of the aldehyde as the major product for all electron donating group substituted benzyl derivatives studied. It should be noted that alkyl esters side chains were not observed to yield aldehyde product under any conditions.

4.1.5 Conclusions

In conclusion, a range of α-diazo-β-ketoesters were designed and synthesised, including many novel derivatives. These diazo compounds were designed with particular structural features in an attempt to study the impact of electronic factors on the product distribution following rhodium(II) catalysed decomposition reactions.

Decomposition reactions were carried out under microwave irradiation as well as at reflux and room temperatures, using rhodium(II) acetate catalyst. A wide variety of decomposition products were isolated and characterised, including aldehydes, alkenes and dioxinones.

A number of mechanistic pathways were proposed, including C-H insertion and hydride abstraction. It is suggested that the alkene products observed are formed by C-H insertion to form a β-lactone, which then undergoes decarboxylation to yield functionalised alkenes. Three plausible mechanisms for the formation of aldehydes are proposed; the aldehydes observed in the course of this research may form *via* rearrangement of a β-lactone intermediate by a cycloreversion pathway. Decomposition of dioxinones by an acetal cleavage pathway could also explain how the aldehydes are formed. A hydride abstraction mechanism might provide a route to aldehyde formation by elimination of a ketene. Hydride abstraction could also lead to dioxinone formation *via* a stabilised carbocation intermediate. Another proposed route to dioxinone formation is by C-H insertion to form a β-lactone intermediate, which subsequently undergoes ring-opening and rearrangement to yield the dioxinone product.

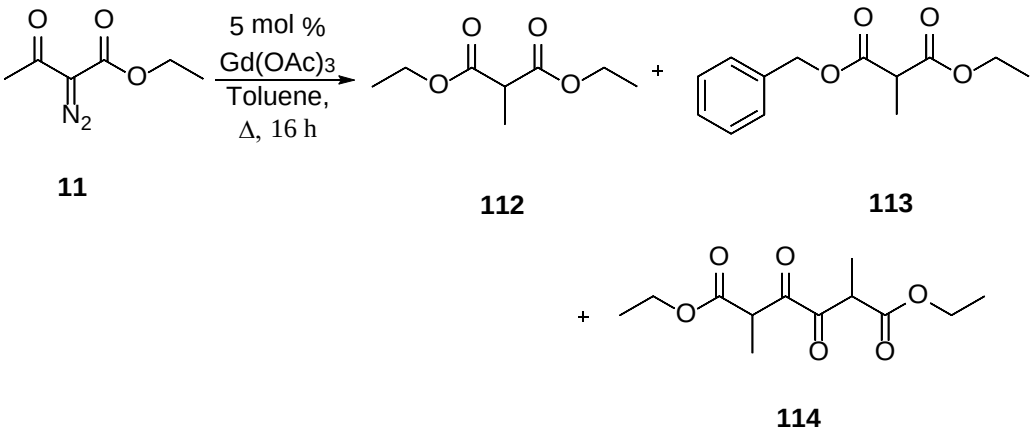
The distribution of these products under various reaction conditions was then analysed and these results were used to determine that C-H insertion of the carbene intermediates is likely to be the major reaction pathway.

4.2 Lanthanide catalysed decomposition of α-diazo-β-ketoesters

4.2.1 Background

Numerous reviews exist in the literature on the use of lanthanide reagents in organic synthesis.[11–23] Lanthanide reagents have been used in place of more traditional reagents in oxidations,[24] reductions,[25] and C-C bond forming reactions.[26] Perhaps the most widely studied class of these reagents are the lanthanide triflates which are used as water compatible Lewis acids.[17,27,28]

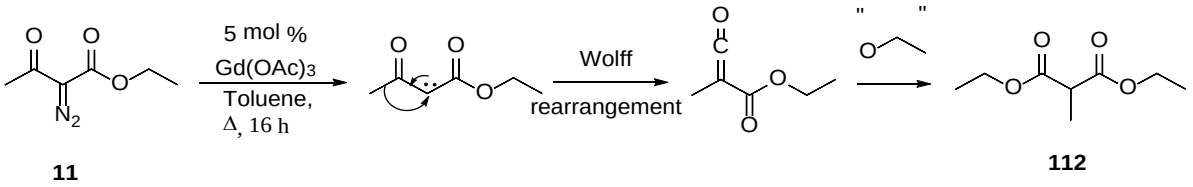
Previous work within the group carried out initial investigations into the reactivity of α-diazo-β-carbonyl compounds under lanthanide catalysis.[1] This previous work investigated various catalysts, catalyst loadings and heating conditions, along with a variety of solvents. It was found that a number of interesting decomposition pathways resulted from the use of a variety of lanthanide catalysts when toluene was used as the reaction solvent. An example of this is shown in **Scheme 4.25** below.



11 **112** **113** **114**

Scheme 4.25

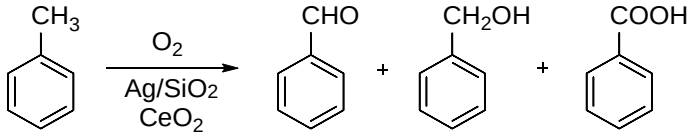
The unusual products **112**, **113** and **114** were isolated from the crude reaction mixture, as can be seen above. It was proposed that products **112** and **114** are formed *via* a Wolff rearrangement mechanism. This is illustrated for **112** in **Scheme 4.26** below.



11 **112**

Scheme 4.26

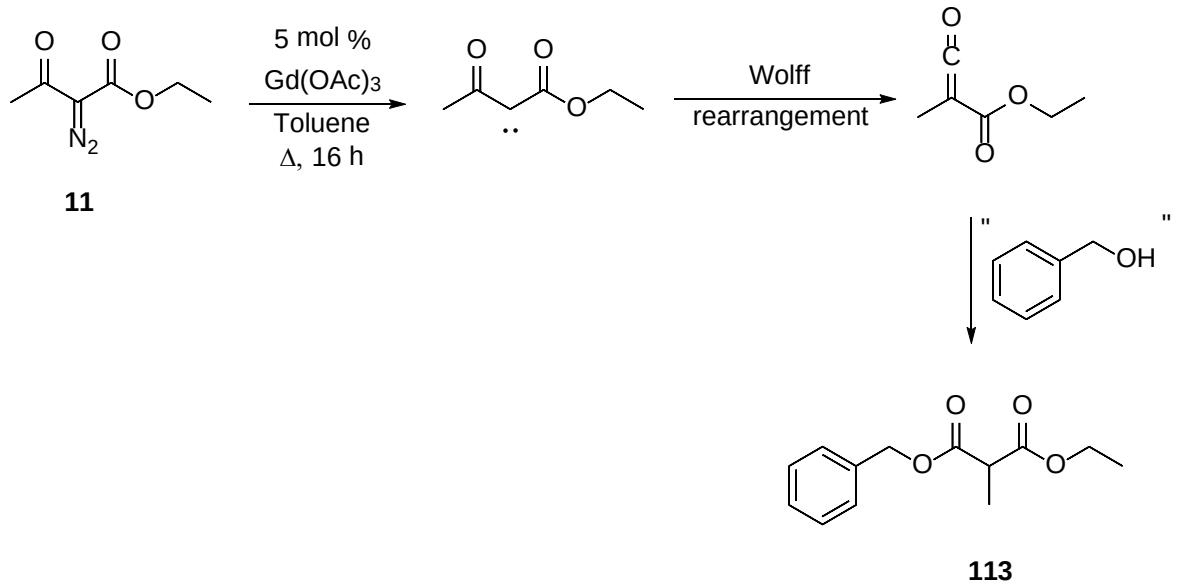
There are reports in the literature of toluene and xylene auto-oxidation in the presence of certain copper and silver catalysts to give a mixture of benzaldehyde **71**, benzyl alcohol **115** and benzoic acid **116** as shown in **Scheme 4.27**.[29–31]



71 **115** **116**

Scheme 4.27

A route by which **113** might be formed was not so apparent, as it appeared to be a benzyl alcohol insertion product, however there is no source of benzyl alcohol in the reaction mixture. Lanthanide-promoted auto-oxidation is a tentative explanation for the formation of **113**, as this could be seen as an insertion of benzyl alcohol, following Wolff rearrangement, as illustrated in **Scheme 4.28**.

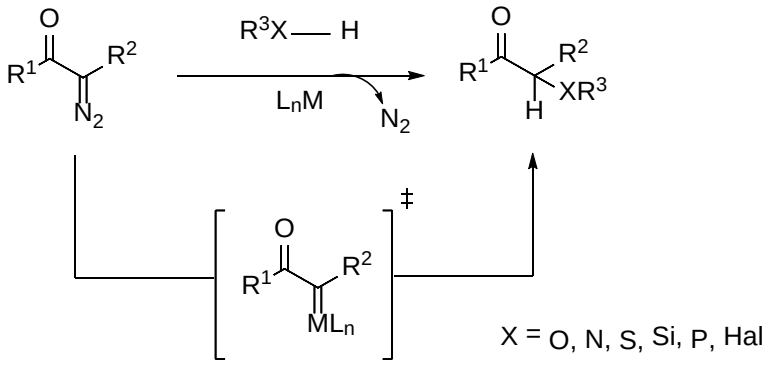


11

113

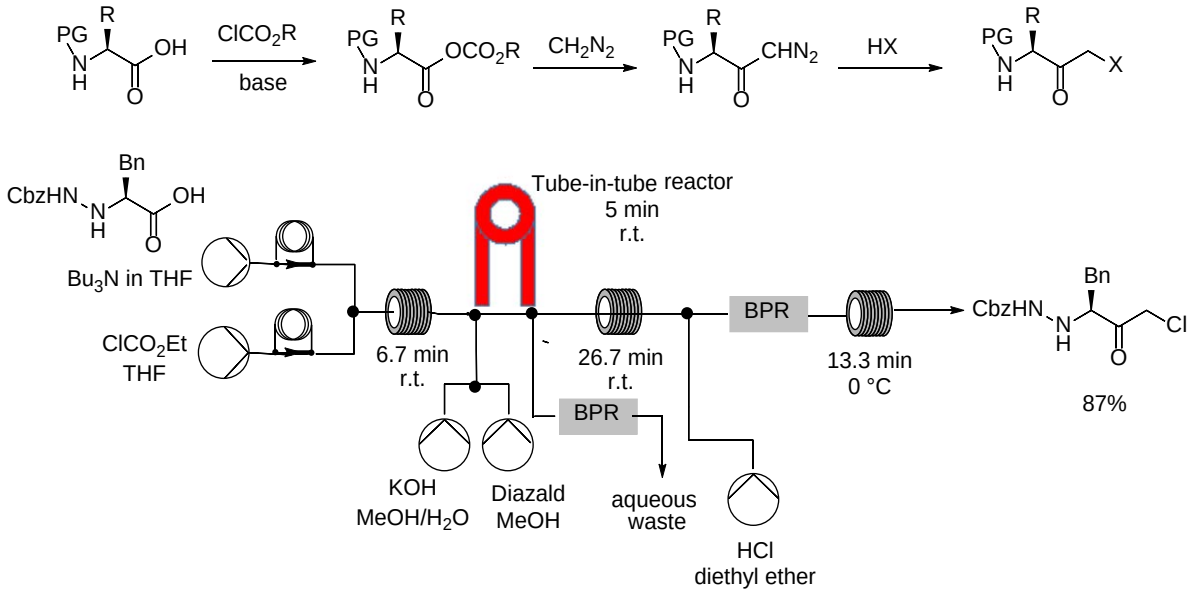
Scheme 4.28

X-H insertion is the insertion of a carbene into the X-H bond, where X is a heteroatom (O, N, S, Si, P, Hal) as can be seen in **Scheme 4.29**. X-H insertion reactions have been widely reviewed in the literature,[32–36] most recently by Gillingham[37] and McKervey.[38]



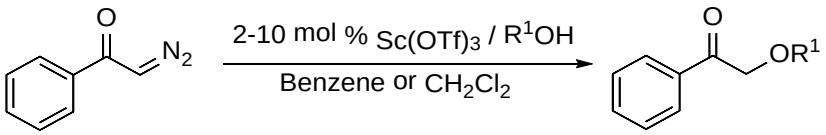
Scheme 4.29

Although these reactions are generally promoted by catalysis, an external catalyst is not always required. Pinho *et al*. developed a continuous flow process for the multistep synthesis of α-halo ketones from *N*-protected amino acids, as illustrated for a phenylalanine derivative in **Scheme 4.30**.[39]



Scheme 4.30

There has been only one report in the literature to date of X-H insertion using lanthanide catalysts and diazocarbonyl compounds. Pansare and co-workers[40] investigated a range of diazocarbonyl insertion reactions into the oxygen-hydrogen bonds as a route to α-alkoxy ketones under mild conditions. The authors reported successful O-H insertions in various alcohols, using scandium triflate (2-10 mol%) as catalyst (**Scheme 4.31**).



Scheme 4.31

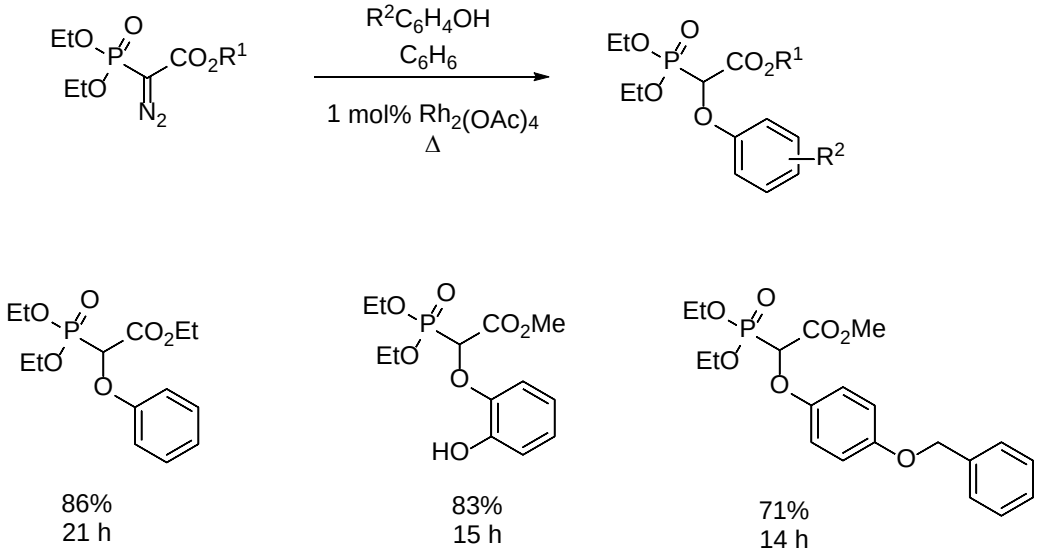
4.2.2 Attempted OH insertion reactions using lanthanide catalysis

O-H insertion reactions have been widely reported in the literature. In a recent review, Gillingham and Fei assembled the table shown below in **Figure 4.16**.[37] As can be seen, many different transition metals have been used to effect insertion reactions, but copper and rhodium remain the most widely used catalysts for the reactions.

Fe	Co	Ni	Cu
Ru	Rh	Pd	Ag
Os	Ir	Pt	Au

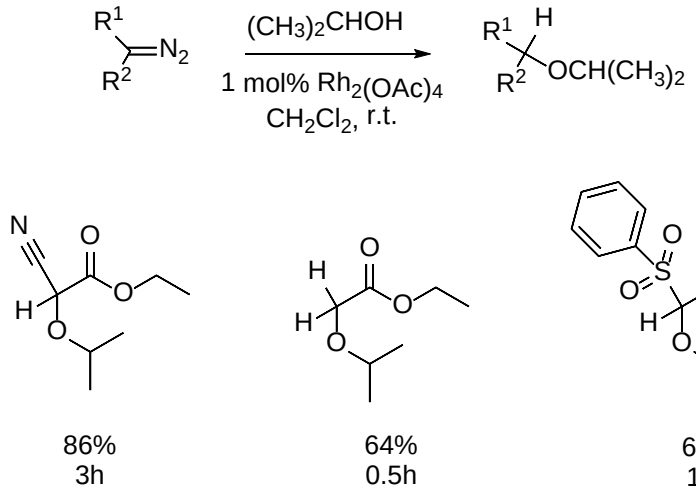
Figure 4.16 Metals for carbenoid reactions – the font scaling conveys the effectiveness of each metal. Reproduced from Ref 32.

Haigh reported rhodium carbenoid O-H insertion reactions with phenols as part of SmithKline Beecham's research into the preparation of 2-aryloxy-3-phenylpropanoates.[41] The author reported successful rhodium(II) catalysed O-H insertion reactions with a variey of substituted phenols and diazophosphonoacetates as shown in **Scheme 4.32**.



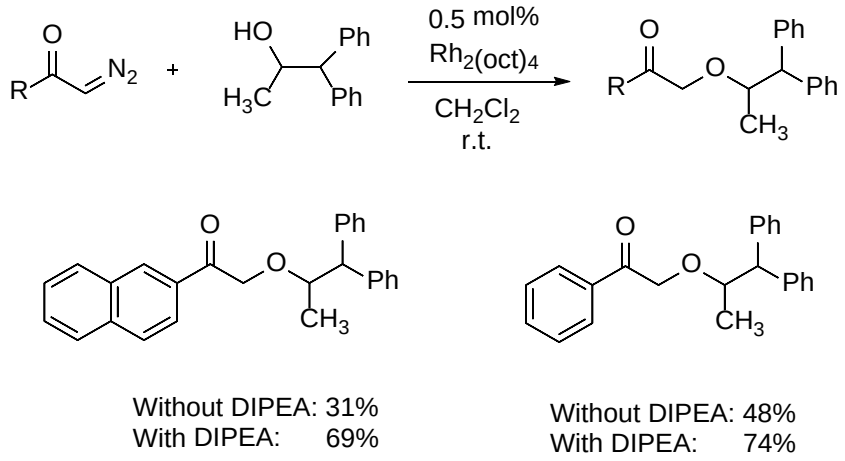
Scheme 4.32

Moody and co-workers reported rhodium(II) catalysed O-H insertion with a selection of diazo compounds with various electron withdrawing groups, as shown in **Scheme 4.33**.[42] The authors found that α-diazosulfones and α-diazocarbonyl compounds reacted most efficiently to form O-H insertion products.



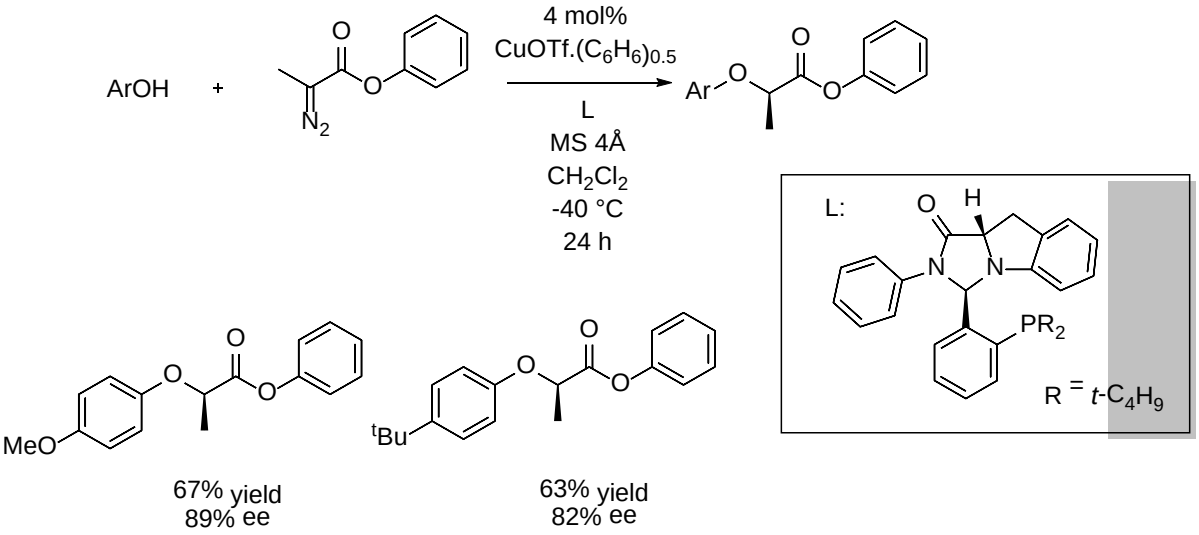
Scheme 4.33

Merck reported the use of rhodium(II) mediated O-H insertion as part of a synthesis of ascomycin derivatives.[43] The authors reported a dramatic increase in the quantity of O-H insertion product isolated for the reactions outlined in **Scheme 4.34** below when DIPEA was used as an additive.



Scheme 4.34

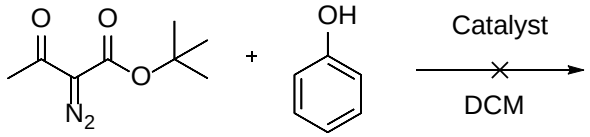
Copper catalysis has also been used to facilitate O-H insertion reactions. Osako *et al*. reported enantioselective carbenoid insertion into phenolic O-H bonds with a chiral copper(I) imidazoindolephosphine complex, as shown in **Scheme 4.35**.[44] The α-aryloxypropionate products were synthesised and good yields and high enantioselectivity using this method.



Scheme 4.35

It was decided to investigate the use of lanthanide catalysts in O-H insertion reactions. A selection of lanthanide catalysts were chosen based on their commercial availability. *t*-Butyl 2-diazo-3-oxobutanoate **12** was chosen as a model diazo compound to carry out initial investigations with. Reactions were typically carried out on a 1 mmol scale, at both room temperature and reflux using various loadings of gadolinium(III) acetate [$Gd(OAc)_3$] as catalyst. A large excess of the chosen alcohol, phenol **117** was used. Reaction monitoring was carried out by TLC analysis. **Table 4.18** below summarises the results obtained in the initial screen. Unfortunately, no reaction was observed in any case, with starting material only recovered. Dichloromethane was chosen as solvent instead of toluene, as it is a good microwave conductor, and we wished to suppress possible toluene auto-oxidation products seen when similar experiments were carried out within the group, as outlined in **Section 4.2.1**.

Table 4.18 ***Lanthanide-catalysed decompositions - Gd(OAc)$_3$***



12 **117**

Entry[a]	Catalyst	Conditions	Temperature °C	Catalyst Loading (mol %)	Time h	Result
1	$Gd(OAc)_3$	r.t.	25	1	48	No reaction
2	$Gd(OAc)_3$	r.t.	25	5	48	No reaction
3	$Gd(OAc)_3$	r.t.	25	10	48	No reaction
4	$Gd(OAc)_3$	Δ	45	1	19.5	No reaction
5	$Gd(OAc)_3$	Δ	45	5	24	No reaction
6	$Gd(OAc)_3$	Δ	45	10	24	No reaction

[a] Reactions typically carried out on a 1mmol scale in dichloromethane.

Subsequent reactions attempted used gadolinium(III) acetate in DCM under microwave irradiation at 100 °C for 3 minutes. These conditions were attempted with both 1 and 5 mol% catalyst loading. Phenol **117** was added in a stoichiometric quantity for these reactions. After a reaction time of three minutes, a ^{1}H NMR spectrum of the crude reaction mixture was obtained. Encouragingly, traces of decomposition products were observed in the ^{1}H NMR spectra of both crude reaction mixtures, although large amounts of starting material were also visible. Disappointingly, only starting material was isolated from both reactions following column chromatography on silica gel.

Following on from disappointing results obtained with gadolinium(III) acetate, the next catalyst used for these reactions was erbium(III) triflate [$Er(OTF)_3$]. When the decomposition reaction was done with 1 mol% catalyst at room temperature, TLC analysis showed evidence

of phenol **117** remaining after 48 h, along with two new spots. When a ^{1}H NMR spectrum of the crude reaction mixture was obtained, evidence was observed for several decomposition products. Column chromatography on silica gel yielded unreacted phenol **117**, as well as two decomposition products, 2-(*t*-butyl)phenol **118** in 8% yield, and 2-oxopropyl 2-diazo-3-oxobutanoate **119** in 30% yield (**Table 4.19**). These products were completely unexpected but were assigned using HMBC and HSQC NMR studies, and confirmed by mass spectrometry. The ^{1}H NMR spectrum of **119** and **118** are shown below in **Figures 4.17** and **4.18** respectively. **118** is commercially available from Sigma Aldrich,[45] and **119** is a known compound in the literature.[46] The spectral details of both compounds match the literature values.

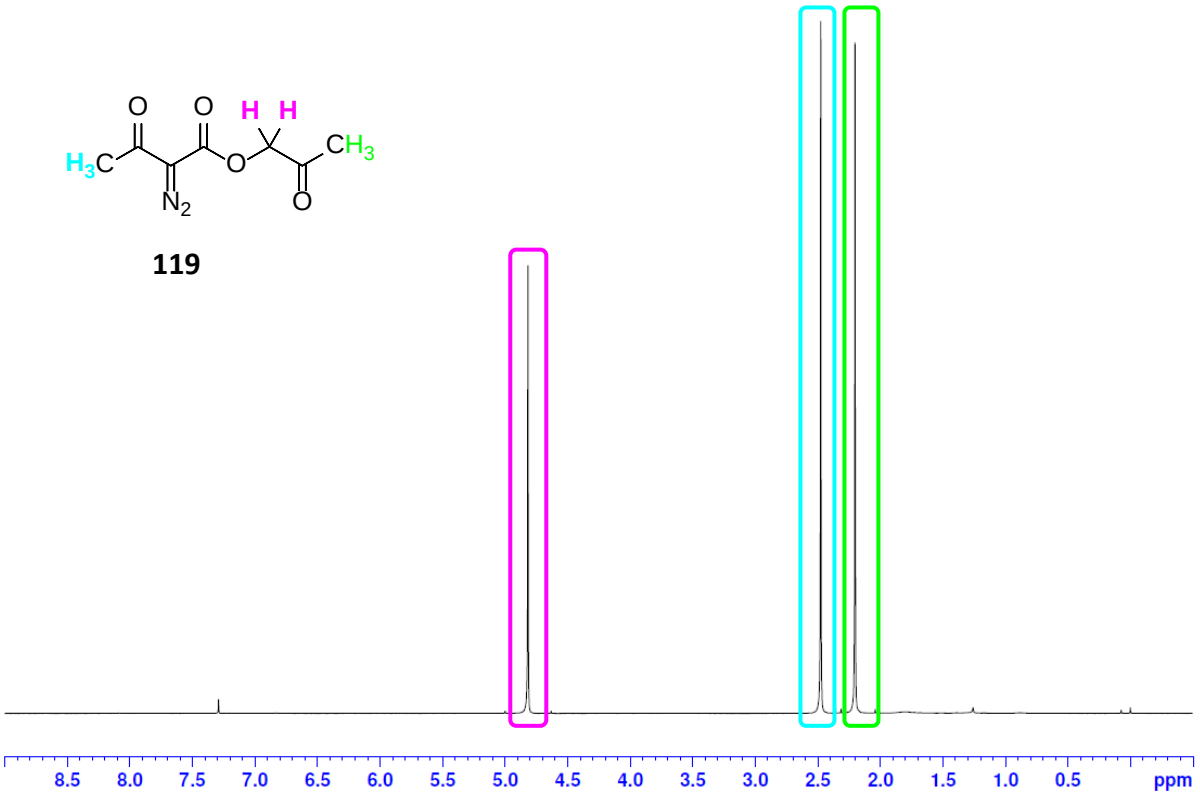


Figure 4.17 ^{1}H NMR spectrum of 2-oxopropyl 2-diazo-3-oxobutanoate **119**.

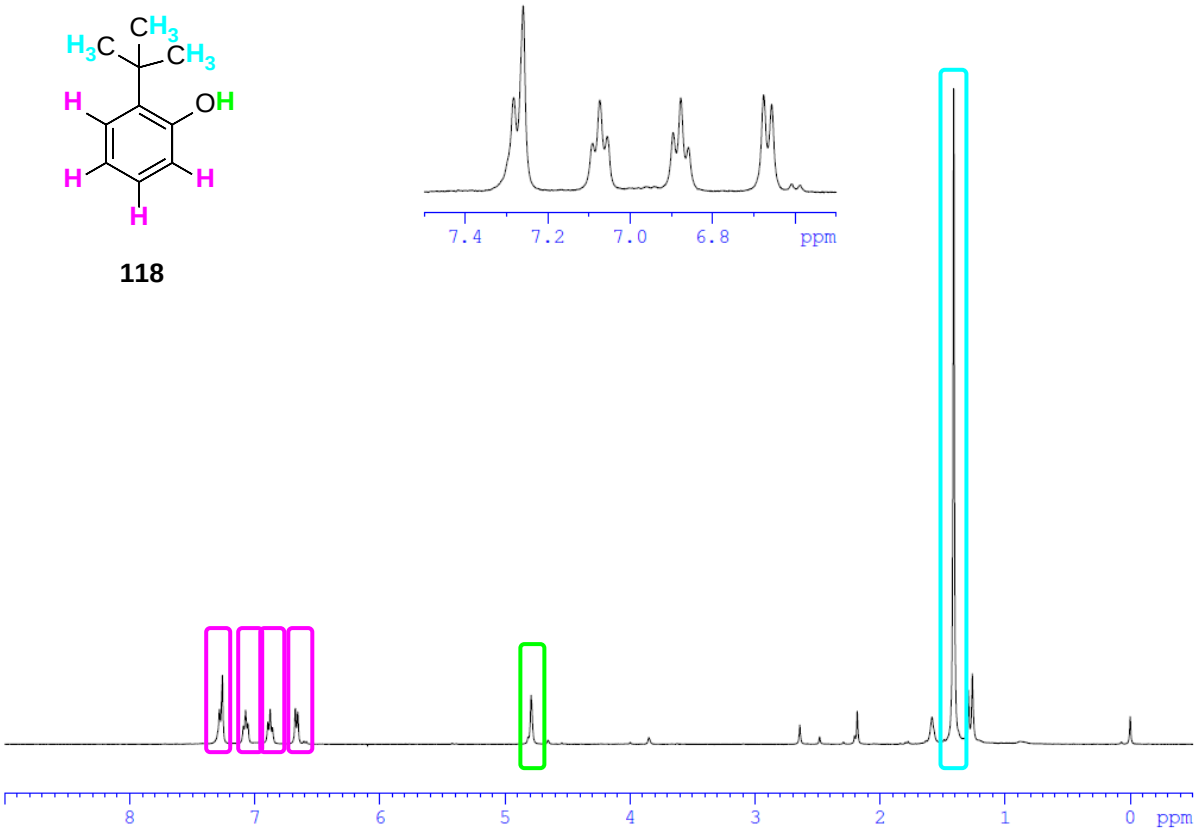


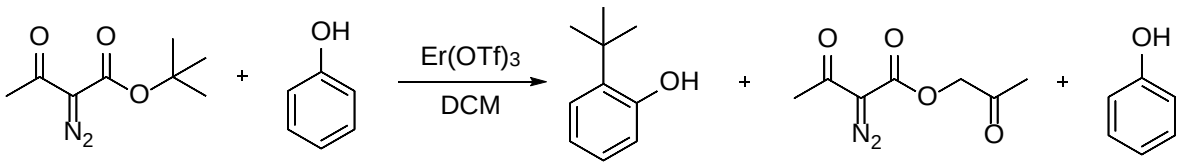
Figure 4.18 ^{1}H NMR spectrum of 2-(*t*-butyl)phenol **118**.

The above reaction was carried out under several different conditions, with various temperatures, reaction times and temperatures, as outlined in **Table 4.19** below. Comparing Entries 1 and 2 we can see that, at room temperature, when the base loading is increased from 1 to 5 mol% the quantity of **118** yielded increases from 8 to 20%, while the quantity of **119** present is the same with both base loadings. In contrast to this, Entry 3 shows that 15% of **118** and 18% of **119** were isolated from the crude reaction mixture when 1 mol% erbium(III) triflate was used at the higher temperature of 45 °C in conjunction with a shorter reaction time. Interestingly, when the catalyst loading was increased to 5 mol% under the same reaction conditions, only 13% of **118** and 27% of **119** were isolated from the crude reaction mixture.

When microwave irradiation was used to promote decomposition in the presence of 1 mol% erbium(III) triflate, neither decomposition product was isolated from the crude reaction

mixture, although evidence of some decomposition products can be seen in the ^{1}H NMR of the crude reaction mixture. Increasing the catalyst loading to 5 mol% resulted in the formation of **119** in 24% yield. There was no evidence observed for the formation of **118** under these conditions.

Table 4.19 ***Lanthanide-catalysed decompositions - Er(OTf)$_3$***



12 **117** **118** **119** **117**

Entry	Catalyst Loading (mol %)	Conditions	Temperature °C	Time	% 118[1]	% 119[1]	% 117[1]
1	1	r.t.	25	48 h	8	30	65
2	5	r.t.	25	48 h	20	30	56
3	1	Δ	45	24 h	15	18	63
4	5	Δ	45	24 h	13	27	59
5	1	MW	100	3 min	-	-	53
6	5	MW	100	3 min	-	24	59

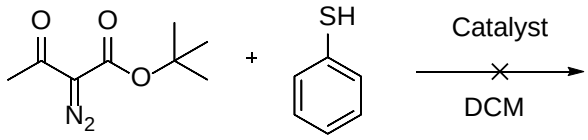
[1] Isolated yields after column chromatography on silica gel.

It is apparent from the above results that O-H insertion is not a reaction pathway of the lanthanide catalysed decomposition reaction conditions outlined above. Erbium(III) triflate instead gives rise to new decomposition products from those previously reported when similar reactions have been carried out using rhodium or copper catalysis. Future work will involve exploring the new reaction pathways from a synthetic and mechanistic viewpoint.

4.2.3 Attempted S-H insertion reactions using lanthanide catalysis

S-H insertion reactions were also attempted in the course of this research. This was done by using thiophenol **120** in place of phenol **117** in reactions similar to those outlined above. Reactions using several different loadings of gadolinium(III) acetate, with different reaction times and heating conditions were done, as outlined in **Table 4.20** below. Disappointingly, the ^{1}H NMR spectra of the crude reaction mixtures for each of the reactions outlined in **Table 4.20** showed 100% starting material.

Table 4.20 ***Lanthanide-catalysed decompositions - Gd(OAc)$_3$***



12 **120**

Entry[a]	Catalyst	Conditions	Temperature °C	Catalyst Loading (mol %)	Time	Result
1	$Gd(OAc)_3$	r.t.	25	1	78 h	No reaction
2	$Gd(OAc)_3$	r.t.	25	5	78 h	No reaction
3	$Gd(OAc)_3$	Δ	45	1	24 h	No reaction
4	$Gd(OAc)_3$	Δ	45	5	24 h	No reaction
5	$Gd(OAc)_3$	MW	100	1	3 mins	No reaction
6	$Gd(OAc)_3$	MW	100	5	3 mins	No reaction
7	$Gd(OAc)_3$	MW	100	10	40 mins	10% **121**

When the above reaction was carried out using 10 mol% gadolinium(III) acetate under microwave irradiation an interesting result was obtained. This reaction was carried out for a significantly increased reaction time of 40 minutes. This was to test if applying more forcing conditions would yield a product similar to 2-oxopropyl 2-diazo-3-oxobutanoate **119**, or any other decomposition products. When a ^{1}H NMR spectrum of the crude reaction mixture was obtained, evidence of small quantities of decomposition products were observed. Following repeated column chromatography, *S,S*-diphenyl 2-methylpropanebis(thioate) **121** was isolated in 10% yield. Although this is an unexpected product from this reaction, NMR spectroscopy was used to propose a structure which was later confirmed by mass spectrometry (**Figure 4.19**).

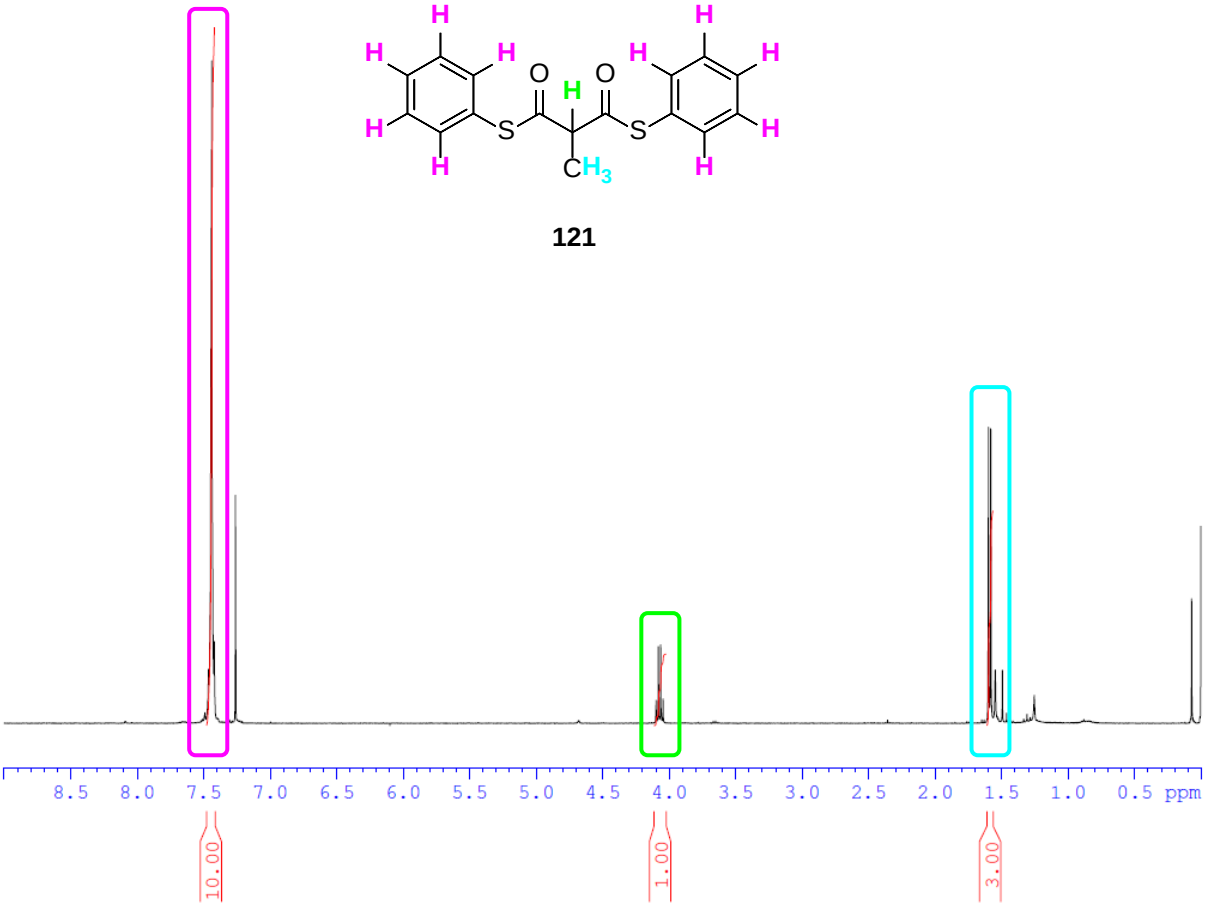
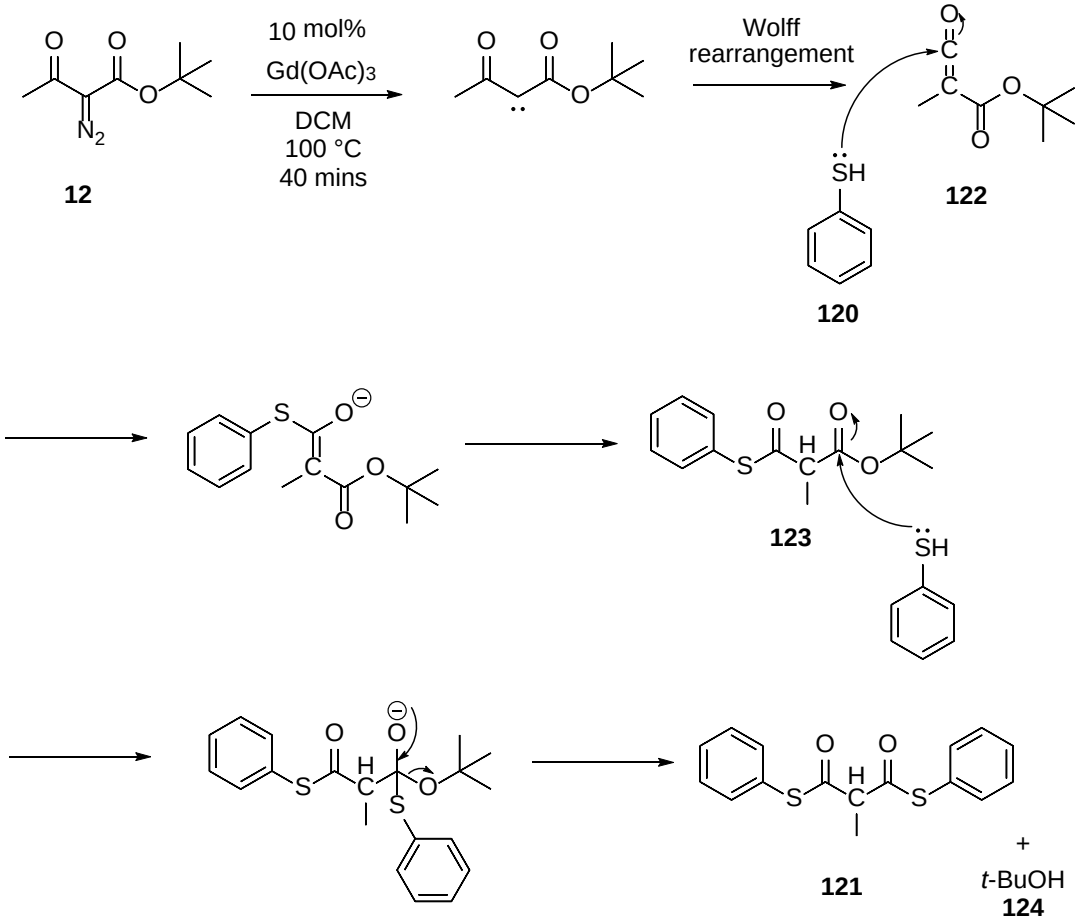


Figure 4.19 ^{1}H NMR spectrum of **121**.

A plausible mechanism is proposed for the formation of *S,S*-diphenyl 2-methylpropanebis(thioate) **121** in **Scheme 4.36** below. We propose that gadolinium(III) acetate promotes loss of nitrogen to form the free carbene, which then undergoes Wolff rearrangement following migration of the methyl group. This results in the formation of the ketene intermediate **122** which undergoes nucleophilic attack by thiophenol **120** to yield the mono-thiolated compound **123**. A second nucleophilic attack by another molecule of thiophenol **120** results in the formation of **121** with the elimination of *t*-butanol **124**.

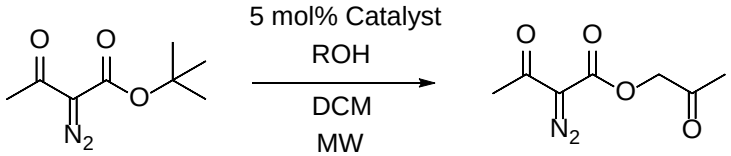


Scheme 4.36

4.2.4 Studies on reactivity using various catalysts under microwave irradiation

It was decided to carry out a screen with various lanthanide catalysts under microwave irradiation conditions. 2-Oxopropyl 2-diazo-3-oxobutanoate **119** had previously been formed under microwave irradiation for 3 minutes in 24% isolated yield. Therefore a reaction time of 10 minutes was chosen, to see if a longer reaction time promoted a greater yield. The reactions were carried out with and without phenol **117** present in the reaction mixture, the results of which are outlined below in **Table 4.21**.

Table 4.21 ***Lanthanide-catalysed decompositions under microwave irradiation – variety of catalysts***



12 **119**

Entry	Catalyst	ROH	% 119
1	-	-	-
2	$Gd(OAc)_3$	-	-
3	$Gd(OAc)_3$	Phenol	-
4	$Gd(OTf)_3$	-	26%
5	$Gd(OTf)_3$	Phenol	30%
6	$Er(OTf)_3$	-	27%
7	$Er(OTf)_3$	Phenol	30%
8	$Yb(OTf)_3$	-	32%
9	$Yb(OTf)_3$	Phenol	30%

As can be seen be seen above, an initial experiment was carried out heating *t*-butyl 2-diazo-3-oxobutanoate **12** in the absence of a catalyst to confirm that the catalyst was playing a role

in the reaction (**Table 4.21**, Entry 1). Only starting material was recovered after 10 minutes superheating in the microwave.

Entries 2 and 3 above report that, either with or without the presence of phenol **117**, no decomposition took place when *t*-butyl 2-diazo-3-oxobutanoate **12** was heated in the presence of gadolinium (III) acetate. This is not unsurprising when previous results obtained when using this catalyst are reviewed.

When gadolinium(III) triflate was used to catalyse these reactions, 2-oxopropyl 2-diazo-3-oxobutanoate **119** was isolated in 26% and 30% yields from the crude reaction mixtures of the reactions outlined in Entries 4 and 5 respectively. This was the first case in which 2-oxopropyl 2-diazo-3-oxobutanoate **119** was observed to form without phenol present in the reaction mixture. When this is viewed in conjunction with the very similar yields for both experiments (**Table 4.21**, Entries 4 and 5), this suggests that phenol doesn't play a role in the formation of **119** and thus is not necessary to include in the reaction.

Erbium(III) triflate was also used as a catalyst (**Table 4.21**, Entries 6 and 7). In the presence and absence of phenol **117**, **119** was isolated in 30 and 27% yields respectively. It is interesting to note that when the initial experiments were carried out (**Table 4.19**, pg 306) 24% yield of **119** was isolated from the crude reaction mixture when *t*-butyl 2-diazo-3-oxobutanoate **12** was heated in the presence of erbium triflate in the microwave for three minutes. An increased reaction time therefore results in an increased yield of **119**.

Use of ytterbium(III) triflate also resulted in the formation of 2-oxopropyl 2-diazo-3-oxobutanoate **119** when reacted under microwave irradiation for ten minutes both in the presence and absence of phenol (**Table 4.21**, Entries 8 and 9).

From the results summarised in **Table 4.21**, we can conclude definitively that phenol **117** plays no role in the formation of **119**, as it is formed in similar quantities in the presence and absence of **117**. We can also conclude that although gadolinium(III) acetate is an ineffective catalyst for these reaction, lanthanide triflates such as gadolinium(III) triflate, erbium(III) triflate and ytterbium(III) triflate do promote reactivity of α-diazo-β-ketoesters by loss of nitrogen to generate of a carbene, followed by rearrangement to form **119**.

The next step in this research was to investigate if other α-diazo-β-ketoesters yielded similar decomposition products to those we had observed to date. Therefore a selection of diazo compounds, shown in **Figure 4.20**, were subjected to microwave irradiation in the presence of 5 mol% erbium(III) triflate for 20 minutes. Unfortunately and surprisingly, in all cases, the ^{1}H NMR spectra of the crude reactions mixtures showed no reaction had occurred. Due to time constraints towards the end of the end of the project erbium(III) triflate was the only catalyst used to investigate these reactions. Erbium(III) triflate was chosen as it had consistently resulted in decomposition under all reaction conditions. Future work in this area will include extensive investigations using a variety of diazo compounds, catalysts, catalyst loadings and heating conditions.

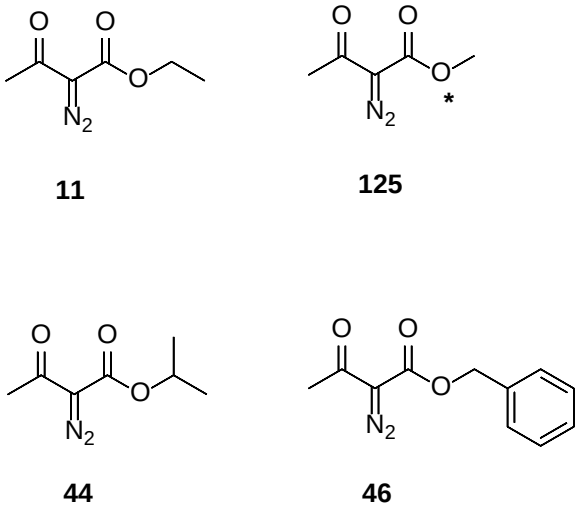


Figure 4.20 α-Diazo-β-keotesters subjected to lanthanide catalysis. Compound marked with ***** kindly supplied by another member of the group.

4.2.5 Conclusions

To conclude, O-H and S-H insertion reaction pathways were not observed in any of the lanthanide catalysis reactions carried out in the course of this research. When attempting O-H insertion, it was determined that gadolinium(III) acetate did not promote any decomposition of *t*-butyl 2-diazo-3-oxobutanoate **12**.

Lanthanide triflates such as erbium(III) triflate, gadolinium(III) triflate and ytterbium(III) triflate gave rise to two unusual decomposition products when used as catalysts for diazo decomposition of *t*-butyl 2-diazo-3-oxobutanoate **12.** 2-(*t*-Butyl)phenol **118** and 2-oxopropyl 2-diazo-3-oxobutanoate **119** were isolated under erbium (III) triflate decomposition under room temperature and reflux conditions. 2-Oxopropyl 2-diazo-3-oxobutanoate **119** was isolated using a variety of lanthanide triflate catalysts under microwave conditions.

Initial S-H insertion reactions were also attempted but proved unsuccessful in all cases. However, a Wolff rearrangement product, *S,S*-diphenyl 2-methylpropanebis(thioate) **121** was isolated when gadolinium(III) acetate was used as catalyst for decomposition of *t*-butyl 2-diazo-3-oxobutanoate **12** under harsh microwave conditions.

Disappointingly, to date no other diazo derivatives other than *t*-butyl 2-diazo-3-oxobutanoate **12** have been successfully decomposed to the products above using lanthanide catalysis.

4.3 References

[1] E. Tarrant, New Insights into the Synthesis of α-Diazocarbonyl Compounds and Their Decomposition Pathways, PhD Thesis, University College Cork, **2012**.

[2] R. H. Tale, A. D. Sagar, H. D. Santan, R. N. Adude, *Synlett* **2006**, 415–418.

[3] S. B. Solabannavar, U. V Desai, R. B. Mane, *Indian J. Chem. Sect. B Org. Chem. Incl. Med. Chem.* **2004**, *43B*, 2235–2237.

[4] H. Valizadeh, E. Khalili, *J. Iran. Chem. Soc.* **2012**, *9*, 529–534.

[5] J. B. Hendrickson, W. A. Wolf, *J. Org. Chem.* **1968**, *33*, 3610–3618.

[6] J. S. Clark, A. G. Dossetter, Y.-S. Wong, R. J. Townsend, W. G. Whittingham, C. A. Russell, *J. Org. Chem.* **2004**, *69*, 3886–3898.

[7] M. P. Doyle, A. B. Dyatkin, C. L. Autry, *J. Chem. Soc. Perkin Trans. 1* **1995**, 619–621.

[8] D. J. Wardrop, R. E. Forslund, *Tetrahedron Lett.* **2002**, *43*, 737–739.

[9] C. H. Yoon, A. Nagle, C. Chen, D. Gandhi, K. W. Jung, *Org. Lett.* **2003**, *5*, 2259–2262.

[10] G. Chelucci, N. Culeddu, A. Saba, R. Valenti, *Tetrahedron Lett.* **1999**, *40*, 8269–8270.

[11] K. A. Choquette, R. A. Flowers, in *Compr. Org. Synth. (2nd Ed.)*, Elsevier B.V., **2014**, pp. 278–343.

[12] T. Imamoto, *Kagaku, Zokan (Kyoto)* **1995**, *124*, 55–61.

[13] T. Imamoto, *Kidorui* **1995**, *27*, 79–95.

[14] H. B. Kagan, J. L. Namy, *Tetrahedron* **1986**, *42*, 6573–6614.

[15] H. B. Kagan, *Chem. Rev.* **2002**, *102*, 1805–1806.

[16] H. B. Kagan, M. Sasaki, J. Collin, *Pure Appl. Chem.* **1988**, *60*, 1725–1730.

[17] S. Kobayashi, *European J. Org. Chem.* **1999**, 15–27.

[18] S. Kobayashi, *Top. Organomet. Chem.* **1999**, *2*, 63–118.

[19] S. Kobayashi, in *Handb. Phys. Chem. Rare Earths*, Elsevier, **2000**, pp. 315–375.

[20] S. Kobayashi, in *Aqueous-Phase Organomet. Catal. (2nd Ed.)*, Wiley-VCH Verlag GmbH & Co. KGaA, **2004**, pp. 88–99.

[21] G. A. Molander, *Chem. Rev.* **1992**, *92*, 29–68.

[22] G. A. Molander, in *Chem. Met.-Carbon Bond*, Wiley, **1989**, pp. 319–396.

[23] P. G. Steel, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2727–2751.

[24] T. Ogata, Y. Sugiyama, S. Ito, K. Nakano, E. Torii, A. Nishiuchi, T. Kimachi, *Tetrahedron* **2013**, *69*, 10470–10476.

[25] J. D. White, G. L. Larson, *J. Org. Chem.* **1978**, *43*, 4555–4556.

[26] G. B. Dudley, D. A. Engel, I. Ghiviriga, H. Lam, K. W. C. Poon, J. A. Singletary, *Org. Lett.* **2007**, *9*, 2839–2842.

[27] S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209–217.

[28] S. Kobayashi, *Chem. Lett.* **1991**, 2187–2190.

[29] X. Wang, J. Wu, M. Zhao, Y. Lv, G. Li, C. Hu, *J. Phys. Chem. C* **2009**, *113*, 14270–14278.

[30] G. Huang, F. Xiang, T.-M. Li, Y.-X. Jiang, Y.-A. Guo, *Catal. Commun.* **2011**, *12*, 886–889.

[31] M. J. Beier, B. Schimmoeller, T. W. Hansen, J. E. T. Andersen, S. E. Pratsinis, J.-D. Grunwaldt, *J. Mol. Catal. A Chem.* **2010**, *331*, 40–49.

[32] M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919–940.

[33] W. F. Ferstl, M. S. Schwarzer, S. L. Loebbecke, *Chemie Ing. Tech.* **2004**, *76*, 1326–1327.

[34] T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160.

[35] Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577-6605.

[36] T. Doyle, M. P.; McKervey, M. A.; Ye, *Modern Catalytic Methods in Organic Synthesis with Diazo Compunds, from Cyclopropanes to Ylides*, John Wiley And Sons Inc.: New York, **1998**.

[37] D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918-4931.

[38] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981–10080.

[39] V. D. Pinho, B. Gutmann, L. S. M. Miranda, R. O. M. A. de Souza, C. O. Kappe, *J. Org. Chem.* **2014**, *79*, 1555–1562.

[40] S. V Pansare, R. P. Jain, A. Bhattacharyya, *Tetrahedron Lett.* **1999**, *40*, 5255–5258.

[41] D. Haigh, *Tetrahedron* **1994**, *50*, 3177–3194.

[42] G. G. Cox, D. J. Miller, C. J. Moody, E. R. H. B. Sie, J. J. Kulagowski, *Tetrahedron* **1994**, *50*, 3195–3212.

[43] T. D. Nelson, Z. J. Song, A. S. Thompson, M. Zhao, A. DeMarco, R. A. Reamer, M. F. Huntington, E. J. J. Grabowski, P. J. Reider, *Tetrahedron Lett.* **2000**, *41*, 1877–1881.

[44] T. Osako, D. Panichakul, Y. Uozumi, *Org. Lett.* **2012**, *14*, 194–197.

[45] Commercially available from Sigma Aldrich, CAS no. 88-18-6.

[46] D. C. Dean, K. E. Krumpe, A. Padwa, *J. Chem. Soc. Chem. Commun.* **1989**, 921–922.

Chapter 4

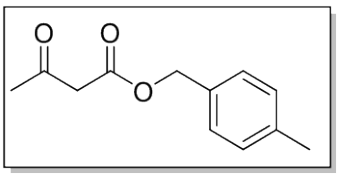
Experimental

Table of Contents

4.1 Synthesis of α-diazocarbonyl compounds

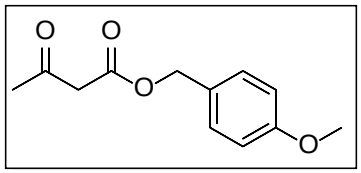
4.1.1 Preparation of ester derivatives

Note: Non-commercial esters were prepared by transesterification with 3-nitrobenzeneboranic acid.[1] Despite repeated column chromatography, ~10% of the enol tautomer is present in the sample. Characteristic signals for the enol form are present at 5ppm in the ^{1}H NMR spectrum and at 22, 63, 90, 173 and 176 ppm in the ^{13}C NMR spectrum for these samples.



4-Methylbenzyl 3-oxobutanoate[2] 50

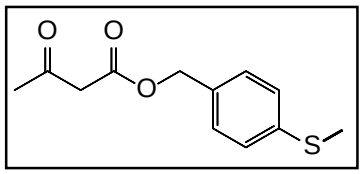
4-Methylbenzyl alcohol **126** (2.01 g, 16.45 mmol) was added to a stirring solution of ethyl acetoacetate **9** (2.14 g, 16.45 mmol) in toluene (50 mL). 3-Nitrobenzeneboronic acid **8** (69 mg, 411 µmol, 2.5 mol %) was then added as catalyst. The reaction was heated under reflux (150 °C) overnight with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. TLC analysis after 18 h indicated complete consumption of the ethyl acetoacetate **9** and, after cooling, the toluene was removed under reduced pressure to give the product, 4-methylbenzyl 3-oxobutanoate **50** as a yellow oil (3.61 g, 94%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 2.22 [3H, s, C*H*$_3$C(O)], 2.34 (3H, s, C*H*$_3$ on aryl ring), 3.46 [2H, s, C(O)C*H*$_2$C(O)], 5.12 (2H, s, OC*H*$_2$), 7.15-7.17 (2H, m, 2 x Ar-*H*), 7.23-7.25 (2H, m, 2 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 21.2 (*C*H$_3$), 30.1 (*C*H$_3$), 50.1 [C(O)*C*H$_2$C(O)], 67.1 (O*C*H$_2$), 128.6 (2 x *o*-Ar-*C*H), 129.3 (2 x *m*-Ar-*C*H), 132.3 (C_q-CH$_3$), 138.4 (C_q), 166.9 (*C*=O) ester, 200.4 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 3009, 1740, 1714; HRMS (ES+): Exact mass calculated for $C_{12}H_{14}O_3Na$ $[M+Na]^+$ 229.0835. Found 229.0834; *m/z* (ES+) 229.3 [(M +Na), 100 %].



4-Methoxybenzyl 3-oxobutanoate[3] **51**

The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 4-methoxybenzyl alcohol **75** (2.60 g, 18.79 mmol), ethyl acetoacetate **9** (2.45 g, 18.79 mmol) and 3-nitrobenzeneboronic acid **8** (78 mg, 470 µmol, 2.5 mol %) in toluene (60 mL). The reaction was heated under reflux for 18 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus, and, after cooling, the toluene was removed under reduced pressure. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (70:30) as eluent, 4-methoxybenzyl 3-oxobutanoate **51** was isolated as a pale yellow oil (4.00 g, 96 %). δ_H($CDCl_3$, 400 MHz): 2.23 [3H, s, C*H*$_3$C(O)], 3.47 [2H, s, C(O)C*H*$_2$C(O)], 3.80 (3H, s, OC*H*$_3$), 5.11 (2H, s, OC*H*$_2$), 6.86-6.95 (2H, m, 2 x Ar-*H*), 7.28-7.35 (2H, m, 2 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 30.1 (*C*H$_3$), 50.1 [C(O)*C*H$_2$C(O)], 55.3 (O*C*H$_3$), 66.9 (O*C*H$_2$), 114.0 (2 x Ar-*C*H), 127.4 (C_q), 130.3 (2 x Ar-*C*H), 159.8 (C_q-OCH$_3$), 167.0 (*C*=O) ester, 200.5 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1738, 1713; HRMS (ES+): Exact mass calculated for $C_{12}H_{14}O_4Na$ $[M+Na]^+$ 245.0784. Found 245.0785; *m/z* (ES+) 245.3 [(M +Na), 90 %], *m/z* (ES-) 221.3 [(M -H), 100 %].

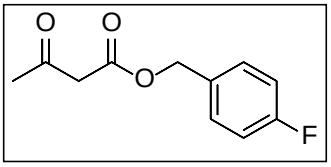
Spectral characteristics were consistent with those previously reported.[3]



4-(Methylthio)benzyl 3-oxobutanoate 52

The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 4-(methylthio)benzyl alcohol **129** (2.44 g, 15.80 mmol), ethyl acetoacetate **9** (2.06 g, 15.80 mmol) and 3-nitrobenzeneboranic acid **8** (66 mg, 395 µmol, 2.5 mol %) in toluene (50 mL). The reaction was heated under reflux for 18 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. Following purification of the crude product by repeated chromatography on silica gel, using hexane-ethyl acetate (70:30) as eluent, 4-(methylthio)benzyl 3-oxobutanoate **52** was isolated as a pale yellow oil (2.94 g, 78 %). δ_H($CDCl_3$, 400 MHz): 2.23 [3H, s, C*H*$_3$C(O)], 2.47 (3H, s, SC*H*$_3$), 3.47 [2H, s, C(O)C*H*$_2$C(O)], 5.12 (2H, s, OC*H*$_2$), 7.18-7.3 (4H, m, 4 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 15.6 (S*C*H$_3$), 30.2 (*C*H$_3$), 50.0 [C(O)*C*H$_2$C(O)], 66.8 (O*C*H$_2$), 126.5 (2 x Ar-*C*H), 129.1 (2 x *o*-Ar-

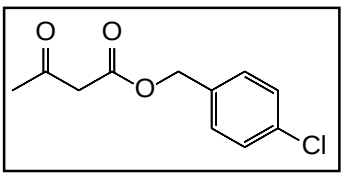
*C*H), 131.9 (C_q), 139.2 (C_q-SCH_3), 166.9 (*C*=O) ester, 200.4 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1739, 1713; HRMS (ES+): Exact mass calculated for $C_{12}H_{14}O_3SNa$ $[M+Na]^+$ 261.0556. Found 261.0557; *m/z* (ES+) 261.2 [(M +Na), 30 %], *m/z* (ES-) 237.3 [(M -H), 100 %].



4-Fluorobenzyl 3-oxobutanoate[4] **53**

The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 4-fluorobenzyl alcohol **127** (1.59 g, 12.65 mmol), ethyl acetoacetate **9** (1.65 g, 12.65 mmol) and 3-nitrobenzeneboranic acid **8** (52 mg, 316 µmol, 2.5 mol %) in toluene (60 mL). The reaction was heated under reflux for 18 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (70:30) as eluent, 4-fluorobenzyl 3-oxobutanoate **53** was isolated as an oil (2.39 g, 90 %). δ_H($CDCl_3$, 400 MHz): 2.26 [3H, s, C*H*$_3$C(O)], 3.49 [2H, s, C(O)C*H*$_2$C(O)], 5.14 (2H, s, OC*H*$_2$), 7.00-7.08(2H, m, 2 x Ar-*H*), 7.31-7.38 (2H, m, 2 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 30.3 (*C*H$_3$), 49.8 [C(O)*C*H$_2$C(O)], 65.5 (O*C*H$_2$), 123.8 (2 x Ar-*C*H), 128.5 (2 x Ar-*C*H), 142.6 (C_q), 147.8 (C_q), 166.6 (*C*=O) ester, 200.0 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1742, 1715; ; HRMS (ES+): Exact mass calculated for $C_{11}H_{12}O_3F$ $[M+H]^+$ 211.0770. Found 211.0764; *m/z* (ES+) 233.3 [(M +Na), 90 %], *m/z* (ES-) 209.3 [(M -H), 30 %].

Spectral characteristics were consistent with those previously reported.[4]

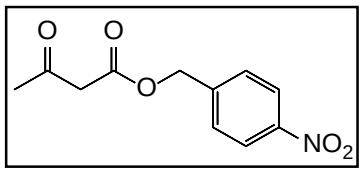


4-Chlorobenzyl 3-oxobutanoate [5] **54**

The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 4-chlorobenzyl alcohol **128** (2.19 g, 15.36 mmol), ethyl acetoacetate **9** (1.99 g, 15.36 mmol) and 3-nitrobenzeneboranic acid **8** (64 mg, 384 µmol, 2.5 mol %) in toluene (60 mL). The reaction was heated under reflux for 20 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (70:30) as eluent, 4-chlorobenzyl 3-oxobutanoate **54** was isolated as a yellow oil (3.04 g, 87 %). δ_H($CDCl_3$, 400

MHz): 2.24 [3H, s, C*H*$_3$C(O)], 3.49 [2H, s, C(O)C*H*$_2$C(O)], 5.13 (2H, s, OC*H*$_2$), 7.26-7.35 (4H, m, 4 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 30.2 (*C*H_3), 49.9 [C(O)*C*H_2C(O)], 66.2 (O*C*H_2), 128.8 (2 x Ar-*C*H), 129.7 (2 x Ar-*C*H), 133.8 (C_q), 134.4 (C_q), 166.8 (*C*=O) ester, 200.2 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1741, 1714; HRMS (ES+): Exact mass calculated for $C_{11}H_{12}ClO_3$ $[M+H]^+$ 227.0475. Found 227.0473; *m/z* (ES+) 249.2 [($C_{11}H_{11}O_3Cl^{35}$ +Na), 100 %], 251.2 [($C_{11}H_{11}O_3Cl^{37}$ +Na), 40 %].

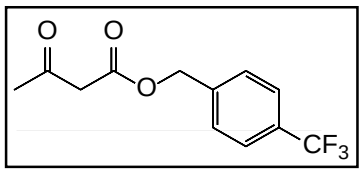
Spectral characteristics were consistent with those previously reported.[5]



4-Nitrobenzyl 3-oxobutanoate[6] **55**

The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 4-nitrobenzyl alcohol **130** (2.02 g, 13.20 mmol), ethyl acetoacetate **9** (1.72 g, 13.20 mmol) and 3-nitrobenzeneboranic acid **8** (55 mg, 330 µmol, 2.5 mol %) in toluene (60 mL). The reaction was heated under reflux for 20 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (60:40) as eluent, 4-nitrobenzyl 3-oxobutanoate **55** was isolated as a pale yellow solid (2.88 g, 92 %), mp 44-46 °C, Lit[6] mp 44-45 °C. Found C 55.46, H 4.70, N, 6.37%; $C_{11}H_{11}O_5N$ requires C 55.70, H 4.67, N 5.90%; δ_H($CDCl_3$, 400 MHz): 2.29 (3H, s, C*H*$_3$), 3.59 [2H, s, C(O)C*H*$_2$C(O)], 5.28 (2H, s, OC*H*$_2$), 7.52-7.59 (2H, m, 2 x Ar-*H*), 8.19-8.27 (2H, m, 2 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 30.3 (*C*H_3), 49.8 [C(O)*C*H_2C(O)], 65.5 (O*C*H_2), 123.8 (2 x Ar-*C*H), 128.5 (2 x Ar-*C*H), 142.5 (C_q), 147.9 (C_q), 166.6 (*C*=O) ester, 199.9 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1746, 1715, 1514, 1343; HRMS (ES-): Exact mass calculated for $C_{11}H_{10}NO_5$ $[M-H]^-$ 236.0559. Found 236.0552; *m/z* (ES-) 236.3 [(M -H), 100 %].

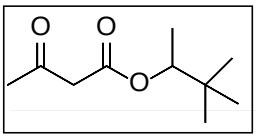
Spectral characteristics were consistent with those previously reported.[6]



4-(Trifluoromethyl)benzyl 3-oxobutanoate[7] **56**

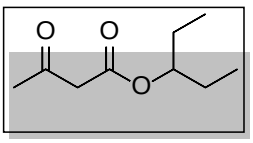
The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 4-(trifluoromethyl)benzyl alcohol **131** (2.73 g, 15.47 mmol), ethyl acetoacetate **9** (2.01 g, 15.47

mmol) and 3-nitrobenzeneboranic acid **8** (65 mg, 387 µmol, 2.5 mol %) in toluene (50 mL). The reaction was heated under reflux for 18 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (70:30) as eluent, 4-(trifluoromethyl)benzyl 3-oxobutanoate **56** was isolated as a colourless oil (3.64 g, 90 %). δ_H($CDCl_3$, 400 MHz) 2.26 (3H, s, C*H*$_3$), 3.53 [2H, s, C(O)C*H*$_2$C(O)], 5.23 (2H, s, OC*H*$_2$), 7.45-7.51 (2H, m, 2 x Ar-*H*), 7.60-7.67 (2H, m, 2 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 30.2 (*C*H$_3$), 49.9 [C(O)*C*H$_2$C(O)], 66.0 (O*C*H$_2$), 125.6 (2 x Ar-*C*H), 127.9 (*C*$_q$), 128.3 (2 x Ar-*C*H), 130.6 (q, *C*F$_3$, $^1J_{CF}$ 320 Hz), 139.3 (*C*$_q$), 166.7 (*C*=O) ester, 200.1 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1745, 1717; HRMS (ES+): Exact mass calculated for $C_{12}H_{12}O_3F_3$ $[M+H]^+$ 261.0739. Found 261.0732; *m/z* (ES+) 283.2 [(M +Na), 100 %], *m/z* (ES-) 259.3 [(M -H), 100 %].



3,3-Dimethylbutan-2-yl 3-oxobutanoate[8] **57**

The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 3,3-dimethyl-2-butanol **132** (1.18 g, 11.54 mmol), ethyl acetoacetate **9** (1.50 g, 11.54 mmol) and 3-nitrobenzeneboranic acid **8** (48 mg, 289 µmol, 2.5 mol %) in toluene (50 mL). The reaction was heated under reflux for 22 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. The reaction was cooled and the toluene removed under reduced pressure to give a clear oil. Following purification on silica gel using 80:20 hexane:ethyl acetate, 3,3-dimethylbutan-2-yl 3-oxobutanoate **57** was obtained as a pale yellow oil (1.89 g, 88 %). δ_H($CDCl_3$, 400 MHz): 0.91 (9H, s, 3 x C*H*$_3$ of *t*-butyl), 1.17 (3H, d, OCHC*H*$_3$, *J* 6.1), 2.28 [3H, s, C*H*$_3$C(O)], 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.74 (1H, q, OCHC*H*$_3$, *J* 6.3); δ_C($CDCl_3$, 100 MHz): 14.8 (*C*H$_3$), 25.6 (3 x *C*H$_3$ of *t*-butyl group), 30.1 (*C*H$_3$), 34.1 [*C*(CH$_3$)$_3$], 50.4 [C(O)*C*H$_2$C(O)], 79.1 [CO*C*(CH$_3$)], 166.7 (*C*=O) ester, 200.6 (*C*=O) ketone. ν_{max}(ATR)/cm^{-1} 1740, 1715; HRMS (ES+): Exact mass calculated for $C_{10}H_{18}O_3Na$ $[M+Na]^+$ 209.1148. Found 209.1144; *m/z* (ES+) 209.3 [(M +Na), 100 %].

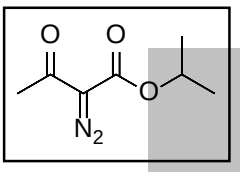


Pentan-3-yl 3-oxobutanoate[9] **58**

The title compound was prepared following the procedure described for 4-methylbenzyl 3-oxobutanoate **50** using 3-pentanol **133** (1.02 g, 11.59 mmol), ethyl acetoacetate **9** (1.51 g, 11.59 mmol) and 3-nitrobenzeneboranic acid **8** (48 mg, 290 µmol, 2.5 mol %) in toluene (60 mL). The reaction was heated under reflux for 18 h with the toluene-ethanol azeotrope continuously removed from the reaction using a Dean-Stark distillation apparatus. Following purification of the crude product by chromatography on silica gel, using hexane-ethyl acetate (80:20) as eluent, pentan-3-yl 3-oxobutanoate **58** was isolated as a pale yellow oil (1.99 g, 80 %). δ_H($CDCl_3$, 400 MHz): 0.89 (6H, m, 2 x C*H*$_3$), 1.55 – 1.67 (4H, m, 2 x C*H*$_2$), 2.27 (3H, s, C*H*$_3$), 3.45 [2H, s, C(O)C*H*$_2$C(O)], 4.78 – 4.85 (1H, m, OC*H*); δ_C($CDCl_3$, 100 MHz): 9.5 (2 x *C*H$_3$), 26.3 (2 x *C*H$_2$), 30.1 (*C*H$_3$), 50.4 [C(O)*C*H$_2$C(O)], 78.1 (O*C*H), 166.9 (*C*=O) ester, 200.6 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1736, 1715; HRMS (ES+): Exact mass calculated for $C_{10}H_{18}O_3Na$ $[M+Na]^+$ 195.0991. Found 195.0977; *m/z* (ES+) 195.3 [(M +Na), 100 %], *m/z* (ES-) 171.3 [(M-H), 100%].

Spectral characteristics were consistent with those previously reported.[9]

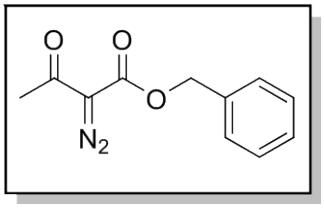
4.1.2 Diazo transfer reactions to β*-ketoesters*



Isopropyl 2-diazo-3-oxobutanoate 44

The title compound was prepared following the procedure described for ethyl 2-diazo-3-oxobutanoate **11** in section **2.2.3** using triethylamine (1.96 mL, 14.07 mmol), isopropyl 3-oxobutanoate **134** (2.03 g, 14.07 mmol) in acetonitrile (35 mL), and a solution of *p*-toluenesulfonyl azide **1** (2.78 g, 14.07 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 18 h TLC analysis showed complete consumption of the ester starting material **134** and the reaction mixture was concentrated under reduced pressure. The resulting cream residue was dissolved in ether (30 mL) and washed with 9 % KOH (3 x 30 mL) followed by brine (1 x 30 mL) and water (1 x 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give isopropyl 2-diazo-3-oxobutanoate **44** was obtained as a yellow oil (1.96 g, 82 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 1.32 (6H, d, 2 x C*H*$_3$, *J*

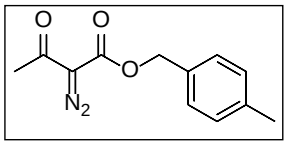
6.4), 2.47 [3H, s, C(O)CH_3], 5.11-5.21 (1H, sept, C*H*, *J* 6.4); δ_C($CDCl_3$, 100 MHz): 21.9 (*C*H_3 x 2 of isopropyl group), 28.1 (*C*H_3), 69.33 (*C*H), 160.9 (*C*=O) ester, 190.1 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max}(film)/cm^{-1} 2140, 1714, 1657; HRMS (ES+): Exact mass calculated for $C_7H_{11}O_3N_2$ $[M+H]^+$ 171.0770. Found 171.0764; *m/z* (ES+) 171.3 [(M+H), 5%], 193.3 [(M +Na), 100 %].



Benzyl 2-diazo-3-oxobutanoate[10] 46

The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (0.39 mL, 2.76 mmol), benzyl 3-oxobutanoate **135** (0.53 g, 2.76 mmol) in acetonitrile (10 mL), and *p*-toluenesulfonyl azide **1** (0.54 g, 2.76 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 16 h TLC analysis showed complete consumption of the ester starting material **135.** Following the work-up benzyl 2-diazo-3-oxobutanoate **46** was obtained as a yellow oil (0.54 g, 89%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 2.46 (3H,s, C*H*$_3$), 5.25 (2H, s, COC*H*$_2$-Ar), 7.28-7.41 (6H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 28.2 (*C*H_3), 66.9 (O*C*H_2), 128.3 (Ar-*C*H), 128.6 (Ar-*C*H), 128.7 (Ar-*C*H), 135.2 (Ar-C_q), 161.23 (*C*=O) ester, 189.9 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max}(ATR)/cm^{-1} 2141, 1698, 1645; HRMS (ES+): Exact mass calculated for $C_{11}H_{11}O_3N_2$ $[M+H]^+$ 219.0770. Found 219.0769; *m/z* (ES+) 241.3 [(M +Na), 70 %].

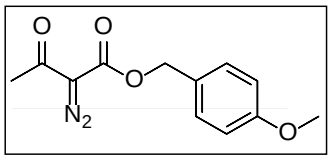
Spectral characteristics were consistent with those previously reported.[10]



4-Methylbenzyl 2-diazo-3-oxobutanoate 59

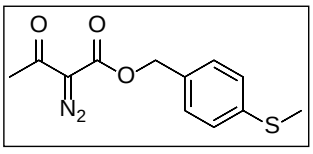
The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (0.17 mL, 1.18 mmol), 4-methylbenzyl 3-oxobutanoate **50** (0.26 g, 1.18 mmol) in acetonitrile (15 mL) and *p*-toluenesulfonyl azide **1** (0.23 g, 1.18 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred at room temperature under an inert nitrogen atmosphere overnight. Following the work-up 4-methylbenzyl 2-diazo-3-oxobutanoate **59** was obtained as a bright yellow solid (0.29 g, 98 %) which was used without further purification, mp 32-34°C. Found C

62.15, H 5.38; $C_{12}H_{12}O_4N_2$ requires C 62.06, H 5.21; δ_H($CDCl_3$, 400 MHz): 2.35 (3H, s, C*H*$_3$), 2.47 (3H, s, Ar-C*H*$_3$), 5.22 (2H, s, COC*H*$_2$-Ar), 7.17-7.19 (2H, m, Ar-*H*), 7.25-7.27 (2H, m, Ar-*H*)); δ_C($CDCl_3$, 100 MHz): 21.2 (*C*H$_3$), 28.2 (Ar-*C*H$_3$), 66.9 (O*C*H$_2$Ar), 128.5 (2 x Ar*C*H), 129.4 (2 x Ar*C*H), 132.2 (ArC_q), 138.6 (ArC_q), 161.3 (*C*=O) ester, 190.1 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max}(ATR)/cm^{-1} 3009, 2138, 1705, 1653; HRMS (ES+): Exact mass calculated for $C_{12}H_{12}O_3N_2Na$ $[M+Na]^+$ 255.0746. Found 255.0734; *m/z* (ES+) 233.3 [(M+H), 8%], 255.3 [(M +Na), 100 %].



4-Methoxybenzyl 2-diazo-3-oxobutanoate[11] **60**

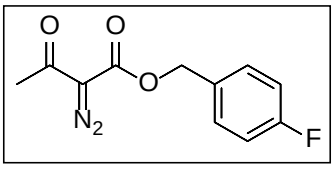
The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (1.25mL, 8.98 mmol), 4-methoxybenzyl 3-oxobutanoate **51** (2.00 g, 8.98 mmol) in acetonitrile (25 mL), and *p*-toluenesulfonyl azide **1** (1.77 g, 8.98 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 18 h TLC analysis showed complete consumption of the ester starting material **51**. Following the work-up 4-methylbenzyl 2-diazo-3-oxobutanoate **60** as a pale yellow solid (1.97 g, 88%), which was used without further purification. Found C 58.08, H 4.94, N, 10.82%; $C_{12}H_{12}O_4N_2$ requires C 58.06, H 4.87, N 11.29%; mp 60-62°C; δ_H($CDCl_3$, 400 MHz): 2.43 (3H, s, C*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 5.16 (2H, s, COC*H*$_2$-Ar), 6.83-6.91 (2H, m, Ar-*H*), 7.25-7.32 (2H, m, Ar-*H*)); δ_C($CDCl_3$, 100 MHz): 28.1 (*C*H$_3$), 55.2 (O*C*H$_3$), 66.7 (O*C*H$_2$Ar), 114.0 (2 x Ar*C*H), 127.3 (ArC_q), 130.3 (2 x Ar*C*H), 159.9 (ArC_q), 161.2 (*C*=O) ester, 189.8 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max}(ATR)/cm^{-1} 3007,2144, 1700, 1649; HRMS (ES+): Exact mass calculated for $C_{12}H_{12}O_4N_2Na$ $[M+Na]^+$ 271.0695. Found 271.0673; *m/z* (ES+) 271.2 [(M +Na), 45 %].



4-(methylthio)benzyl 2-diazo-3-oxobutanoate 61

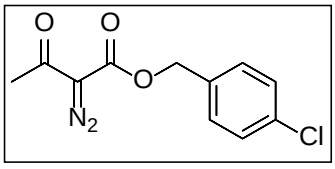
The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (1.48 mL, 10.60 mmol), 4-(methylthio)benzyl 3-oxobutanoate **52** (2.53 g, 10.60 mmol) in acetonitrile (45 mL), and *p*-toluenesulfonyl azide **1** (2.09g, 10.60 mmol) dissolved in

acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 18 h TLC analysis showed complete consumption of the ester starting material. Following the work-up 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** as a yellow solid (2.56 g, 91%), which was used without further purification, mp 48-50°C. Found C 54.45, H 4.51, N 9.86%; $C_{12}H_{12}O_3N_2S$ requires C 54.13, H 4.58, N 10.00%; δ_H($CDCl_3$, 400 MHz): 2.48, 2.49 (3H, s, C*H*$_3$), (3H, s, SC*H*$_3$), 5.22 (2H, s, COC*H*$_2$-Ar), 7.22-7.33 (4H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 15.6 (*C*H$_3$), 28.3 (S*C*H$_3$), 66.7 (O*C*H$_2$Ar), 126.5 (2 x Ar*C*H), 129.1 (2 x Ar*C*H), 131.7 (Ar*C*$_q$), 139.6 (Ar*C*$_q$), 161.3 (*C*=O) ester, 190.0 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max}(ATR)/cm^{-1} 2141, 1713, 1655; HRMS (ES+): Exact mass calculated for $C_{12}H_{13}O_3N_2S$ $[M+H]^+$ 265.0647. Found 265.0657; *m/z* (ES-) 263.3 [(M-H), 10 %].



4-Fluorobenzyl 2-diazo-3-oxobutanoate 62

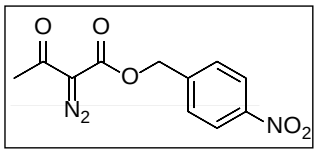
The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (1.45 mL, 10.42 mmol), 4-fluorobenzyl 3-oxobutanoate **53** (2.07 g, 10.42 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **1** (2.05 g, 10.42 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred at room temperature under an inert nitrogen atmosphere overnight. Following the work-up 4-fluorobenzyl 2-diazo-3-oxobutanoate **62** was obtained as a bright yellow oil (1.93 g, 80 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 2.49 (3H, s, C*H*$_3$), 5.37 (2H, s, COC*H*$_2$-Ar), 7.50-7.57 (2H, m, Ar-*H*), 8.20-8.28 (2H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 28.2 (*C*H$_3$), 65.4 (O*C*H$_2$Ar), 76.1 (*C*=N$_2$), 124.0(2 x Ar*C*H), 128.7 (2 x Ar*C*H), 142.3 (Ar*C*$_q$), 148.0 (Ar*C*$_q$), 160.9 (*C*=O) ester, 189.5 (*C*=O) ketone; HRMS (ES+): Exact mass calculated for $C_{11}H_{10}O_3FN_2$ $[M+H]^+$ 237.0675. Found 237.0678; *m/z* (ES+) 237.2 [(M+H), 20%].



4-Chlorobenzyl 2-diazo-3-oxobutanoate 63

The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (1.45 mL, 10.42 mmol), 4-chlorobenzyl 3-oxobutanoate **54** (2.07 g, 10.42 mmol) in acetonitrile (25 mL) and *p*-toluenesulfonyl azide **1** (2.05 g, 10.42 mmol) dissolved in

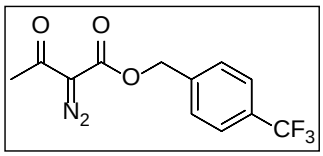
acetonitrile (5 mL). The reaction was stirred at room temperature under an inert nitrogen atmosphere overnight. Following the work-up 4-chlorobenzyl 2-diazo-3-oxobutanoate **63** was obtained as a bright yellow solid, (1.93 g, 80 %), which was used without further purification, mp 111-114°C; δ_H($CDCl_3$, 400 MHz): 2.45 (3H, s, C*H*$_3$), 5.22 (2H, s, COC*H*$_2$-Ar), 7.28-7.38 (4H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 28.2 (*C*H$_3$), 66.0 (O*C*H$_2$Ar), 76.2 (*C*=N$_2$), 128.9 (2 x Ar*C*H), 129.8 (2 x Ar*C*H), 133.7 (Ar*C*$_q$), 134.5 (Ar*C*$_q$), 161.1 (*C*=O) ester, 189.6 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 2145, 1710, 1655; HRMS (ES+): Exact mass calculated for $C_{11}H_{10}O_3N_2Cl^{35}$ $[M+H]^+$ 253.0380. Found 253.0372; *m/z* (ES+) 275.2 [($C_{11}H_9O_3Cl^{35}$ +Na), 100 %], 277.2 [($C_{11}H_{11}O_3Cl^{37}$ +Na), 40 %].



4-Nitrobenzyl 2-diazo-3-oxobutanoate[12] **64**

The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (1.45 mL, 10.40 mmol), 4-nitrobenzyl 3-oxobutanoate **55** (2.47 g, 10.40 mmol) in acetonitrile (35 mL), and *p*-toluenesulfonyl azide **1** (2.05 g, 10.40 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 20 h TLC analysis showed complete consumption of the ester starting material **55**. Following the work-up 4-nitrobenzyl 2-diazo-3-oxobutanoate **64** as a dark yellow solid (2.47g, 91%), which was used without further purification, mp 128-130°C. Found C 50.02, H 3.52, N, 16.19%; $C_{11}H_9O_5N_3$ requires C 50.20, H 3.45, N 15.96%; δ_H($CDCl_3$, 400 MHz): 2.49 (3H, s, C*H*$_3$), 5.36 (2H, s, COC*H*$_2$-Ar), 7.52-7.56 (2H, m, Ar-*H*), 8.23-8.28 (2H, m, Ar-*H*)); δ_C($CDCl_3$, 100 MHz): 28.3 (*C*H$_3$), 65.4 (O*C*H$_2$Ar), 124.0 (2 x Ar*C*H), 128.7 (2 x Ar*C*H), 142.2 (Ar*C*$_q$), 148.0 (Ar*C*$_q$), 160.9 (*C*=O) ester, 189.5 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max}(ATR)/cm^{-1} 2147, 1707, 1660, 1515, 1341, HRMS (ES+): Exact mass calculated for $C_{11}H_{10}N_3O_5$ $[M+H]^+$ 264.0620. Found 264.0629; *m/z* (ES-) 262.3 [(M-H), 10%].

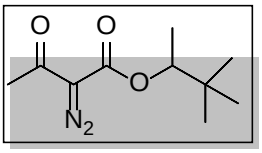
Spectral characteristics were consistent with those previously reported.[12]



4-(Trifluoromethyl)benzyl 2-diazo-3-oxobutanoate 65

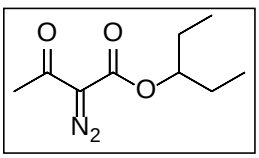
The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using

triethylamine (1.42 mL, 10.14 mmol), 4-(trifluoromethyl)benzyl 3-oxobutanoate **56** (2.64 g, 10.14 mmol) in acetonitrile (40 mL), and *p*-toluenesulfonyl azide **1** (1.99 g, 10.14 mmol) dissolved in acetonitrile (10 mL). The reaction was stirred overnight under an inert nitrogen atmosphere. After 18 h TLC analysis showed complete consumption of the ester starting material **56**. Following the work-up 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65** as a yellow oil (2.53 g, 87%), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 2.49 (3H, s, C*H*$_3$), 5.32 (2H, s, COC*H*$_2$-Ar), 7.46-7.52 (2H, m, Ar-*H*), 7.63-7.69 (2H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 28.3 (*C*H_3), 65.9 (O*C*H_2Ar), 125.7 (Ar*C*$_q$), 125.8 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 130.9 (q, *C*F_3, $^1J_{CF}$ 320 Hz), 139.1 (Ar*C*$_q$), 161.1 (*C*=O) ester, 189.7 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max}(ATR)/cm^{-1} 2149, 1710, 1651; mp 72-74°C. HRMS (ES+): Exact mass calculated for $C_{12}H_{10}N_2O_3F_3$ $[M+H]^+$ 287.0644. Found 287.0657; *m/z* (ES+) 309.2 [(M+Na), 50%], *m/z* (ES-) 285.3 [(M-H), 25%].



3,3-Dimethylbutan-2-yl 2-diazo-3-oxobutanoate 66

The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (0.94 mL, 6.74 mmol), 3,3-dimethylbutan-2-yl 3-oxobutanoate **57** (1.26 g, 6.74 mmol) in acetonitrile (20 mL) and *p*-toluenesulfonyl azide **1** (1.33 g, 6.74 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred at room temperature under an inert nitrogen atmosphere overnight. Following the work-up 3,3-dimethylbutan-2-yl 2-diazo-3-oxobutanoate **66** was obtained as a bright yellow oil (1.29 g, 90 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.93 (9H, s, 3 x C*H*$_3$ of t-butyl), 1.23 (3H, d, OCHC*H*$_3$, *J* 6.5), 2.48 (3H, s, C*H*$_3$), 4.83 (1H, q, OC*H*CH_3, *J* 6.4); δ_C($CDCl_3$, 100 MHz): 15.1 (OCH*C*H_3), 25.6 (3 x *C*H_3 of t-butyl), 29.2 (*C*H_3), 34.3 (*C*$_q$ of t-butyl), 79.4 (O*C*HCH_3), 161.1 (*C*=O) ester, 190.2 (*C*=O) ketone, no signal observed for (*C*=N_2); ν_{max}(ATR)/cm^{-1} 2137, 1711. 1658; Found (HRMS, ESI): Exact mass calculated for $C_{10}H_{16}N_2O_3Na$ $[M+Na]^+$ 235.1059. Found 235.1049; *m/z* (ES+) 235.3 [(M+Na), 100 %].



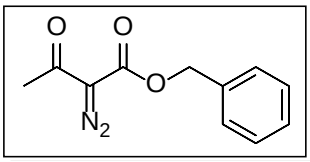
Pentan-3-yl 2-diazo-3-oxobutanoate 67

The title compound was prepared following the procedure described for isopropyl 2-diazo-3-oxobutanoate **44** using triethylamine (0.81 mL,

5.83 mmol), pentan-3-yl 3-oxobutanoate **58** (1.26 g, 6.74 mmol) in acetonitrile (20 mL) and *p*-toluenesulfonyl azide **1** (1.15 g, 5.83 mmol) dissolved in acetonitrile (5 mL). The reaction was stirred at room temperature under an inert nitrogen atmosphere overnight. Following the work-up pentan-3-yl 2-diazo-3-oxobutanoate **67** was obtained as a bright yellow oil (0.94 g, 82 %), which was used without further purification. δ_H($CDCl_3$, 400 MHz): 0.92 (6H, t, 2 x C*H*$_3$, *J* 7.4), 1.59-1.72 (4H, m, 2 x C*H*$_2$), 2.48 (3H, s, C*H*$_3$), 4.87-4.94 (1H, m, OC*H*); δ_C($CDCl_3$, 100 MHz): 9.5 (2 x *C*H$_3$), 26.4 (2 x *C*H$_2$), 28.2 (*C*H$_3$), 78.4 (O*C*H), 161.4 (*C*=O) ester, 190.3 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max}(ATR)/cm^{-1} 2137, 1710, 1657; HRMS (ES+): Exact mass calculated for $C_9H_{15}N_2O_3$ $[M+H]^+$ 199.1083. Found 199.1080; *m/z* (ES+) 199.3 [(M+H), 10%], 221.3 [(M+Na), 100 %].

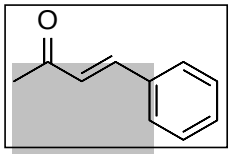
4.2 Rh(II) catalysed decomposition reactions of α-diazo β-ketoesters

4.2.1 Decomposition of benzyl 2-diazo-3-oxobutanoate 46



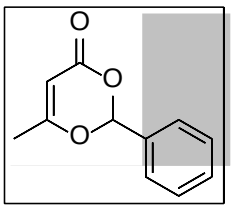
Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

Rhodium(II) acetate dimer (0.16 mg, 0.37 µmol, 0.04 mol %) was added to a stirring solution of benzyl 2-diazo-3-oxobutanoate **46** (0.20 g, 0.92 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 7 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude material shows a complex mixture of products. Purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-60:40) gave two identifiable fractions. The less polar fraction, (*E*)-4-phenylbut-3-en-2-one **70** (38 mg, 28 %) was isolated as a pale yellow oil and the more polar fraction contained 6-methyl-2-phenyl-4H-1,3-dioxin-4-one **69** (23 mg, 13 %) as a clear oil. Evidence for benzaldehyde **71** was seen in the crude reaction mxture but it was not isolated after column chromatography.



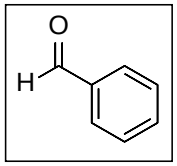
(*E*)-4-Phenylbut-3-en-2-one[43] **70**

δ_H($CDCl_3$, 400 MHz): 2.39 [3H, s, C(O)C*H*$_3$], 6.72 (1H, d, *H*C=C*, J* 16.3), 7.33-7.43 (3H, m, Ar-*H*), 7.51-7.58 [4H, m, containing (1H, d, C=C*H*,), (3H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 27.5 (*C*H_3), 127.2 (Ar-*C*H), 128.3 (2 x Ar-*C*H), 129.0 (2 x Ar-*C*H), 130.6 (*C*H), 134.4 (C_q), 143.5 (*C*H), 198.5 (*C*=O) ketone; ν_{max}(film)/cm^{-1} 1689, 1666; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}O$ $[M+H]^+$ 147.0810. Found 147.0799; *m/z* (ES+) 147.3 [(M+H), 100%].



6-Methyl-2-phenyl-4H-1,3-dioxin-4-one[44] **69**

δ_H($CDCl_3$, 400 MHz): 2.12 (3H, s, C*H*$_3$), 5.43 (1H, s, C*H* alkene), 6.39 (1H, s, OC*H*), 7.31-7.39 (1H, m, Ar-*H*), 7.44-7.49 (2H, m, Ar-*H*), 7.57-7.62 (2H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 19.6 (*C*H_3), 96.5 (*C*H) alkene, 100.0 (O*C*H), 126.6 (2 x Ar-*C*H), 128.6 (2 x Ar-*C*H), 130.4 (*C*H), 133.7 (C_q), 162.2 (C_q) alkene, 172.0 (*C*=O); ν_{max}(ATR)/cm^{-1} 1732, 1629, 1378, 1337; HRMS (ES+): Exact mass calculated for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708. Found 191.0699; *m/z* (ES+) 191.3 [(M+H), 5%], (ES-) 190.2 [(M-H), 5%].



Benzaldehyde[13] **71**

Key signal observed: 1H s at δ_H 10 ppm.

Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

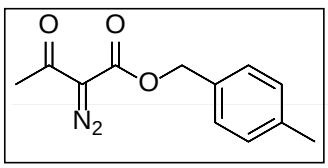
Rhodium(II) acetate dimer (35 mg, 0.08 mmol, 5 mol %) was added to a stirring solution of benzyl 2-diazo-3-oxobutanoate **46** (0.35 g, 1.60 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. The characteristic doublet of (*E*)-4-phenylbut-3-en-2-one **70** at 6.7 ppm is visible in the ^{1}H NMR spectrum of the crude reaction mixture, however there is no evidence of dioxinone formation. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-70:30), one

identifiable fraction was obtained. The fraction contained the (*E*)-4-phenylbut-3-en-2-one **70** as a pale yellow oil (20 mg, 9 %). Evidence for benzaldehyde **71** was seen in the crude reaction mxture but it was not isolated after column chromatography.Spectral details as listed above.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

Rhodium(II) acetate dimer (32 mg, 0.07 mmol, 5 mol %) was added to a solution of benzyl 2-diazo-3-oxobutanoate **46** (0.32 g, 1.45 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **46**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. The characteristic doublet of (*E*)-4-phenylbut-3-en-2-one **70** at 6.7 ppm is visible in the ^{1}H NMR spectrum of the crude reaction mixture, however there is no evidence of dioxinone formation. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-60:40), one identifiable fraction was obtained. The fraction contained the (*E*)-4-phenylbut-3-en-2-one **70** as a pale yellow oil (32 mg, 15 %). Evidence for benzaldehyde **71** was seen in the crude reaction mxture but it was not isolated after column chromatography. Spectral details as listed above.

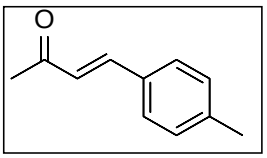
4.2.2 Decomposition of 4-methylbenzyl 2-diazo-3-oxobutanoate 59



Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

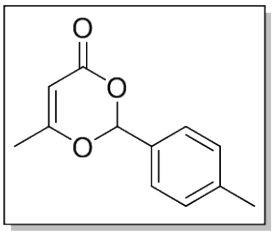
Rhodium(II) acetate dimer (0.2 mg, 0.4 µmol, 0.04 mol %) was added to a solution of 4-methylbenzyl 2-diazo-3-oxobutanoate **59** (0.21 g, 0.99 mmol) in dichloromethane (3 mL). The reaction was heated to 100 °C under microwave irradiation for 3 min, in a sealed microwave tube (pressure ~ 5.6 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure

to give the crude reaction products as a pale brown oil. The ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture of products. Repeated careful column chromatography on silica gel using hexane-ethyl acetate (95:5 – 65:35) gave two identifiable fractions. The less polar fraction, (*E*)-4-(*p*-tolyl)but-3-en-2-one **72** (25 mg, 16 %) was isolated as a clear oil and the more polar fraction contained 6-methyl-2-(*p*-tolyl)-4H-1,3-dioxin-4-one **73** (60 mg, 17 %) as a pale yellow oil. Evidence for 4-methylbenzaldehyde **74** was seen in the crude reaction mxture but it was not isolated after column chromatography.



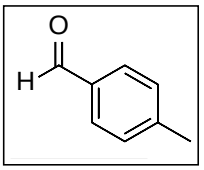
(*E*)-4-(*p*-tolyl)but-3-en-2-one[14] **72**

δ_H($CDCl_3$, 400 MHz): 2.37, 2.38 [3H, s, C(O)C*H*$_3$], [3H, s, Ar-C*H*$_3$), 6.68 (1H, d, *H*C=C*, J* 16.2), 7.18-7.25 (H, m, Ar-*H*), 7.42-7.55 [3H, m, containing (1H, d, C=C*H*), (2H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 27.5 (*C*H$_3$), 127.2 (Ar-*C*H), 128.2 (2 x Ar-*C*H), 128.9 (2 x Ar-*C*H), 129.4 (*C*H), 134.5 (C_q), 143.4 (*C*H), 198.4 (*C*=O) ketone; ν_{max}(film)/cm^{-1} 1663, 1608; HRMS (ES+): Exact mass calculated for $C_{11}H_{13}O$ $[M+H]^+$ 161.0966. Found 161.0963; *m/z* (ES+) 183.3 [(M+Na), 30 %].



6-Methyl-2-(*p*-tolyl)-4H-1,3-dioxin-4-one[15] **73**

δ_H($CDCl_3$, 400 MHz): 2.11 (3H, s, Ar-C*H*$_3$), 2.40 (3H, s, C*H*$_3$), 5.42 (1H, s, C*H* alkene), 6.36 (1H, s, OC*H*), 7.24-7.30 (2H, m, Ar-*H*), 7.44-7.51 (2H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 19.6 (Ar-*C*H$_3$), 21.4 (*C*H$_3$), 96.4 (*C*H) alkene, 100.2 (O*C*H), 126.5 (2 x Ar-*C*H), 129.3 (2 x Ar-*C*H), 130.8 (C_q), 140.5 (C_q), 162.4 (C_q) alkene, 172.1 (*C*=O); ν_{max}(ATR)/cm^{-1} 1719, 1629, 1342;HRMS (ES+): Exact mass calculated for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0865. Found 205.0859; *m/z* (ES+) 205.3 [(M+H), 10%], 227.3 [(M+Na), 30 %].



4-Methylbenzaldehyde[16] **74**

Key signal observed: 1H s at δ_H 9.9 ppm.

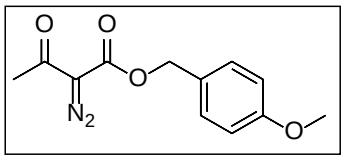
Method 2: Using 5 mol % $Rh_2(OAc)_4$ under reflux for 1.5 h

Rhodium(II) acetate dimer (49 mg, 0.05 mmol, 5 mol %) was added to a stirring solution of 4-methylbenzyl 2-diazo-3-oxobutanoate **59** (0.51 g, 2.22 mmol) in dichloromethane (10 mL). The reaction was heated under reflux for 1.5 h after which time TLC analysis indicated complete consumption of the diazocarbonyl starting material. The reaction mixture was cooled and the dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. Following purification by column chromatography on silica gel, using hexane-ethyl acetate (95:5 – 65:35) as eluent, (*E*)-4-(*p*-tolyl)but-3-en-2-one **72** (38 mg, 11 %) was isolated as a clear oil. 6-Methyl-2-(*p*-tolyl)-4H-1,3-dioxin-4-one **73** (35 mg, 14 %) was isolated as a pale yellow oil. Evidence for 4-methylbenzaldehyde **74** was seen in the crude reaction mxture but it was not isolated after column chromatography. Spectral details as above.

Using 5 mol % $Rh_2(OAc)_4$ at r.t.

Rhodium(II) acetate dimer (22 mg, 0.05 mmol, 5 mol %) was added to a stirring solution 4-methylbenzyl 2-diazo-3-oxobutanoate **59** (0.21 g, 1.01 mmol) in dichloromethane (10 mL) under an inert nitrogen atmosphere. The reaction was stirred at room temperature for 18 h after which time TLC analysis indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a pale green oil. Following purification by column chromatography on silica gel, using hexane-ethyl acetate (95:5 – 65:35) as eluent, (*E*)-4-(*p*-tolyl)but-3-en-2-one **72** (42 mg, 13 %) was isolated as a clear oil. Evidence for 4-methylbenzaldehyde **74** was seen in the crude reaction mxture but it was not isolated after column chromatography.

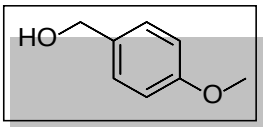
4.2.3 Decomposition of 4-methoxybenzyl 2-diazo-3-oxobutanoate 60



Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

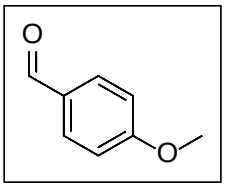
Rhodium(II) acetate dimer (0.15 mg, 0.3 µmol, 0.04 mol %) was added to a stirring solution of 4-methoxybenzyl 2-diazo-3-oxobutanoate **60** (0.21 g, 0.82 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 7 Bar). Vigorous nitrogen gas evolution was observed upon

releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a brown oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-60:40) gave three identifiable fractions. The first fraction, 4-methoxybenzyl alcohol **75** (10 mg, 9 %) was isolated as a clear oil. The second fraction contained 4-methoxybenzaldehyde **76** (11 mg, 10%) as a yellow oil, and the most polar fraction contained 2-(4-methoxyphenyl)-6-methyl-4H-1,3-dioxin-4-one **78** (36 mg, 20 %) as a yellow oil. Evidence for (E)-4-(4-methoxyphenyl)but-3-en-2-one **77** was seen in the crude reaction mxture but it was not isolated after column chromatography.



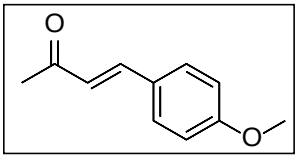
4-Methoxybenzyl alcohol[17] **75**

δ_H($CDCl_3$, 400 MHz): 3.81 (3H, s, OC*H*$_3$), 4.46 (2H, s, C*H*$_2$OH), 6.86-6.91 (2H, m, 2 x Ar-C*H*), 7.25-7.30 (2H, m, 2 x Ar-C*H*); δ_C($CDCl_3$, 100 MHz): 55.3 (O*C*H$_3$), 71.5 (*C*H$_2$OH), 113.8 (2 x Ar-*C*H), 129.4 (2 x Ar-*C*H), 130.5 (Ar-*C*$_q$), 159.2 (Ar-*C*$_q$).



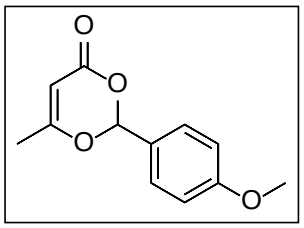
4-Methoxybenzaldehyde[18] **76**

δ_H($CDCl_3$, 400 MHz): 3.89 (3H, s, OC*H*$_3$), 6.98-7.03 (2H, m, 2 x Ar-C*H*), 7.79-7.87 (2H, m, 2 x Ar-C*H*), 9.89 [1H, s, C(O)*H*]; δ_C($CDCl_3$, 100 MHz): 55.6 (O*C*H$_3$), 114.3 (2 x Ar-*C*H), 129.9 (Ar-*C*$_q$), 132.0 (2 x Ar-*C*H), 165.6 (Ar-*C*$_q$), 190.9 (*C*=O); ν_{max}(film)/cm^{-1} 1681, 1596, 1255; HRMS (ES+): Exact mass calculated for $C_8H_9O_2$ $[M+H]^+$ 137.0603. Found 137.0601.



(E)-4-(4-Methoxyphenyl)but-3-en-2-one[19] **77**

Key signal observed: 1H d at δ_H 6.7 ppm.



2-(4-Methoxyphenyl)-6-methyl-4H-1,3-dioxin-4-one[15] **78**

δ_H($CDCl_3$, 400 MHz): 2.10 (3H, s, C*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 5.42 (1H, s, C*H* alkene), 6.34 (1H, s, OC*H*), 6.94-6.99 (2H, m, Ar-*H*), 7.48-7.53 (2H, m, Ar-*H*); δ_C($CDCl_3$, 600 MHz): 19.6 (Ar-*C*H$_3$), 55.4 (O*C*H$_3$), 96.4 (*C*H) alkene, 100.1 (O*C*H), 114.0 (2 x Ar-*C*H), 128.2 (2 x Ar-*C*H), 130.1 (C_q), 161.1 (C_q), 162.5 (C_q) alkene, 172.1 (*C*=O); ν_{max}(film)/cm^{-1} 1732, 1629, 1378, 1337; HRMS (ES+): Exact mass calculated for $C_{12}H_{13}O_4$ $[M+H]^+$ 221.0814. Found 221.0810; *m/z* (ES+) 221.2 [(M+H), 5%].

Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

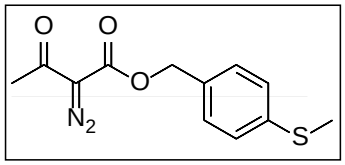
Rhodium(II) acetate dimer (30 mg, 0.08 mmol, 5 mol %) was added to a stirring solution of 4-methoxybenzyl 2-diazo-3-oxobutanoate **60** (0.33 g, 1.33 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (80:20-70:30), two identifiable fractions were obtained. The less polar fraction contained 4-methoxybenzaldehyde **76** (62 mg, 34%) as a yellow oil, while the more polar fraction contained 6-methoxy-2-phenyl-4H-1,3-dioxin-4-one **78** (26 mg, 9 %) as a yellow oil. Evidence for (E)-4-(4-methoxyphenyl)but-3-en-2-one **77** was seen in the crude reaction mxture but it was not isolated after column chromatography. Spectral details as listed above.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

Rhodium(II) acetate dimer (23 mg, 0.05 mmol, 5 mol %) was added to a solution of 4-methoxybenzyl 2-diazo-3-oxobutanoate **60** (0.26 g, 1.04 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **60**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The

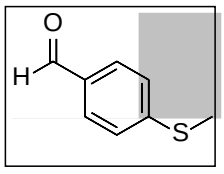
^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-60:40), one identifiable fraction was obtained. The fraction contained the (*E*)- 4-methoxybenzaldehyde **76** (22 mg, 15%) as a yellow oil. Evidence for (E)-4-(4-methoxyphenyl)but-3-en-2-one **77** was seen in the crude reaction mxture but it was not isolated after column chromatography. Spectral details as listed above.

4.2.4 Decomposition of 4-(methylthio)benzyl 2-diazo-3-oxobutanoate 61



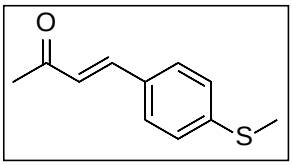
Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

Rhodium(II) acetate dimer (0.15 mg, 0.3 µmol, 0.04 mol %) was added to a stirring solution of 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** (0.21 g, 0.82 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 7 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a purple oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-60:40) gave two identifiable fractions. The first fraction, 4-(methylthio)benzaldehyde **80** (40 mg, 10 %) was isolated as a clear oil. The second fraction contained (*E*)-4-(4-(methylthio)phenyl)but-3-en-2-one **79** (58 mg, 16%) as a pale yellow oil.



4-(Methylthio)benzaldehyde[20] **80**

δ_H($CDCl_3$, 400 MHz): 2.54 (3H, s, OCH_3), 7.31-7.36 (2H, m, 2 x Ar-C*H*), 7.7-7.81 (2H, m, 2 x Ar-C*H*), 9.93 [1H, s, C(O)*H*]; δ_C($CDCl_3$, 100 MHz): 29.6 (S*C*H_3), 114.4 (2 x Ar-*C*H), 131.2 (Ar-C_q), 132.2 (2 x Ar-*C*H), 164.8 (Ar-C_q), 190.7 (*C*=O); ν_{max}(ATR)/cm^{-1} 1692, 1589, 1560; HRMS (ES+): Exact mass calculated for C_8H_9OS $[M+H]^+$ 153.0374. Found 153.0373; *m/z* (ES+) 153.2 [(M+H), 100%].



(*E*)-4-(4-(methylthio)phenyl)but-3-en-2-one 79

δ_H($CDCl_3$, 400 MHz): 2.38 (3H, s, C(O)C*H*$_3$), 2.51 [3H, s, ArSC*H*$_3$], 6.68 (1H, d, *H*C=C*, J* 16.5), 7.22-7.27 (2H, m, Ar-*H*), 7.44-7.49 [3H, m, containing (1H, d, C=C*H*), (2H, m, Ar-*H*)]; δ_C($CDCl_3$, 100 MHz): 15.1 (*C*H$_3$), 27.6 (S*C*H$_3$) 126.2 (2 x Ar-*C*H), 128.6 (2 x Ar-*C*H), 130.9 (*C*$_q$), 142.4 (*C*$_q$), 142.9 (*C*H), 198.4 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1718, 1627, 1517; HRMS (ES+): Exact mass calculated for $C_{11}H_{13}OS$ $[M+H]^+$ 193.0687. Found 193.0680; *m/z* (ES+) 193.3 [(M+H), 100%].

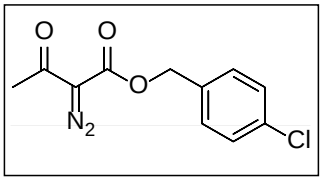
Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

Rhodium(II) acetate dimer (30 mg, 0.08 mmol, 5 mol %) was added to a stirring solution of 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** (0.33 g, 1.25 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min showed complete consumption of **61**. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-75:25), 4-(methylthio)benzaldehyde **80** (57 mg, 30 %) was recovered as a clear oil. Spectral details as listed above.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

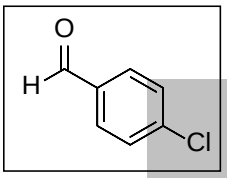
Rhodium(II) acetate dimer (23 mg, 0.05 mmol, 5 mol %) was added to a solution of 4-(methylthio)benzyl 2-diazo-3-oxobutanoate **61** (0.26 g, 1.04 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of **61**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-80:20), 4-(methylthio)benzaldehyde **80** (88 mg, 22 %) was recovered as a clear oil. Spectral details as listed above.

4.2.5 Decomposition of 4-chlorobenzyl 2-diazo-3-oxobutanoate 63



Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

Rhodium(II) acetate dimer (0.35 mg, 0.8 µmol, 0.04 mol %) was added to a stirring solution of 4-chlorobenzyl 2-diazo-3-oxobutanoate **63** (0.49 g, 1.96 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 10 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a brown oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30) gave three identifiable fractions. The first fraction was isolated as a clear oil (102 mg), and has been tentatively assigned as a number of structural fragments based on signals observed in the ^{1}H and ^{13}C NMR spectra, however further investigation and characterisation is required to determine the exact structure of this compound **85**. The second fraction contained (*E*)-4-(4-chlorophenyl)but-3-en-2-one **83** (63 mg, 18 %) was isolated as a clear oil, and the most polar fraction contained 2-(4-chlorophenyl)-6-methyl-4H-1,3-dioxin-4-one **84** (43 mg, 10 %) as a yellow oil. 4-Chlorobenzaldehyde **82** was observed as the major product by ^{1}H NMR in the crude reaction mixture but was not isolated following column chromatography.

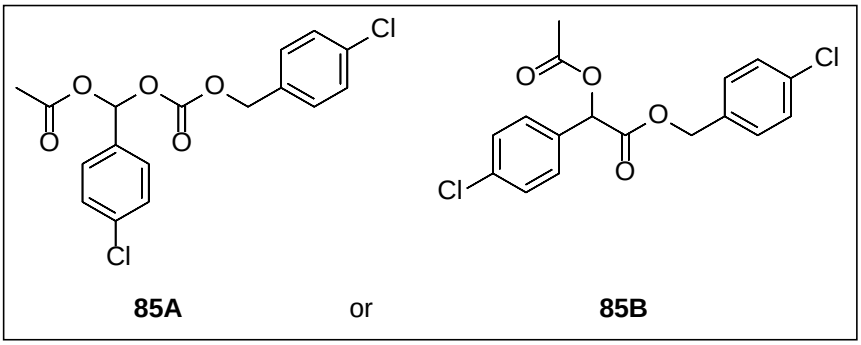


4-Chlorobenzaldehyde[18] **82**

Key signal observed: 1H s at δ_H 10 ppm.

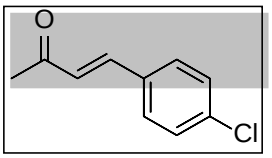
***Tentative assignment of first fraction* 85**

(See **Chapter 4 Results and Discussion**, **Section 4.1.3.6**, **Figure 4.7** for detailed ^{1}H NMR analysis)



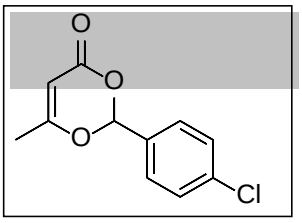
85A or **85B**

δ_H($CDCl_3$, 600 MHz): 2.24 (3H, s, CH_3), 5.23 (2H, apparent quartet, CH_2), 6.69 (1H, s, C*H*), 7.35 -7.48 (8H, m, 8 x Ar-C*H*); δ_C($CDCl_3$, 150 MHz): 11.5 (*C*H_3), 65.5 (*C*H_2), 107.1 (*C*H), 127.8 (2 x Ar-*C*H), 128.8 (2 x Ar-*C*H), 128.9 (2 x Ar-*C*H), 129.8 (2 x Ar-*C*H), 134.1 (C_q), 134.1 (C_q), 134.4 (C_q), 136.2 (C_q), 149.5 (*C*=O), 160.2 (*C*=O); ν_{max}(ATR)/cm^{-1} 1739, 1702, 1493.



(*E*)-4-(4-Chlorophenyl)but-3-en-2-one[21] **83**

δ_H($CDCl_3$, 400 MHz): 2.44 [3H, s, C(O)CH_3], 6.68 (1H, d, *H*C=C*, J* 16.4), 7.34-7.39 (2H, m, Ar-*H*), 7.43-7.49 [3H, m, containing (1H, d, C=C*H*), (2H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 27.7 (*C*H_3), 127.5 (*C*H - alkene), 129.3 (2 x Ar-*C*H), 129.4 (2 x Ar-*C*H), 132.9 (C_q), 136.4 (C_q), 141.9 (*C*H - alkene), 198.1 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1692, 1666, 1597, 1507; HRMS (ES+): Exact mass calculated for $C_{10}H_{10}OCl^{35}$ $[M+H]^+$ 181.0420. Found 181.0416; *m/z* (ES+) 181.3 [($C_{10}H_9OCl^{35}$+H), 100%], 183.3 [($C_{10}H_9OCl^{37}$+H), 40%].



2-(4-Chlorophenyl)-6-methyl-4H-1,3-dioxin-4-one 84

δ_H($CDCl_3$, 400 MHz): 2.12 (3H, s, CH_3), 5.44 (1H, s, C*H* alkene), 6.36 (1H, s, OC*H*), 7.01-7.12 (2H, m, Ar-*H*), 7.50-7.62 (2H, m, Ar-*H*); δ_C($CDCl_3$,100 MHz): 19.5 (*C*H_3), 96.6 (*C*H) alkene, 99.4 (O*C*H), 125.7 (2 x Ar-*C*H), 128.7 (2 x Ar-*C*H), 131.6 (C_q), 141.2 (C_q), 162.0 (C_q alkene), 171.9 (*C*=O); ν_{max}(ATR)/cm^{-1} 1725, 1630, 1462, 1599, 1377; HRMS (ES+): Exact mass calculated for $C_{11}H_{10}O_3Cl$ $[M+H]^+$ 225.0318. Found 225.0320; *m/z* (ES+) 225.2 [(M+H), 35%].

Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

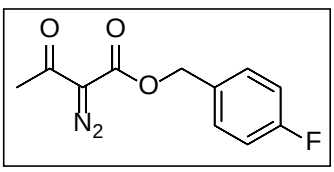
Rhodium(II) acetate dimer (44 mg, 0.1 mmol, 5 mol %) was added to a stirring solution of 4-chlorobenzyl 2-diazo-3-oxobutanoate **63** (0.51 g, 2.00 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen

atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), one identifiable fractions were obtained. This fraction contained (*E*)-4-(4-chlorophenyl)but-3-en-2-one **83** (38 mg, 14 %) as a clear oil. 4-Chlorobenzaldehyde **82** was observed as the major product by ^{1}H NMR in the crude reaction mixture but was not isolated following column chromatography. Spectral details as listed above.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

Rhodium(II) acetate dimer (45 mg, 0.10 mmol, 5 mol %) was added to a solution of 4-chlorobenzyl 2-diazo-3-oxobutanoate **63** (0.51 g, 2.03 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **63**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), one identifiable fractions were obtained. This fraction contained (*E*)-4-(4-chlorophenyl)but-3-en-2-one **83** (51 mg, 14 %) as a clear oil. 4-Chlorobenzaldehyde **82** was observed by ^{1}H NMR in the crude reaction mixture but was not isolated following column chromatography. Spectral details as listed above.

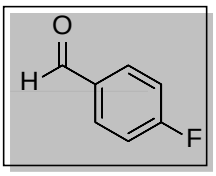
4.2.6 Decomposition of 4-fluorobenzyl 2-diazo-3-oxobutanoate 62



Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

Rhodium(II) acetate dimer (0.03 mg, 0.9 µmol, 0.04 mol %) was added to a stirring solution of 4-fluorobenzyl 2-diazo-3-oxobutanoate **62** (0.51 g, 2.16 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 7 Bar). Vigorous nitrogen gas evolution was

observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a brown oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Purification by chromatography on silica gel using hexane-ethyl acetate (90:10) gave three identifiable fractions. The first fraction was isolated as a clear oil (120 mg), and has been tentatively assigned as a number of structural fragments based on signals observed in the ^{1}H and ^{13}C NMR spectra, however further investigation and characterisation is required to determine the exact structure of this compound **89**. The second fraction contained (*E*)-4-(4-fluorophenyl)but-3-en-2-one **87** (88mg, 25%) as a pale yellow oil, and the most polar fraction contained 2-(4-fluorophenyl)-6-methyl-4H-1,3-dioxin-4-one **88** (36 mg, 8%) as a yellow oil. 4-Fluorobenzaldehyde **86** was observed by ^{1}H NMR in the crude reaction mixture but was not isolated following column chromatography.

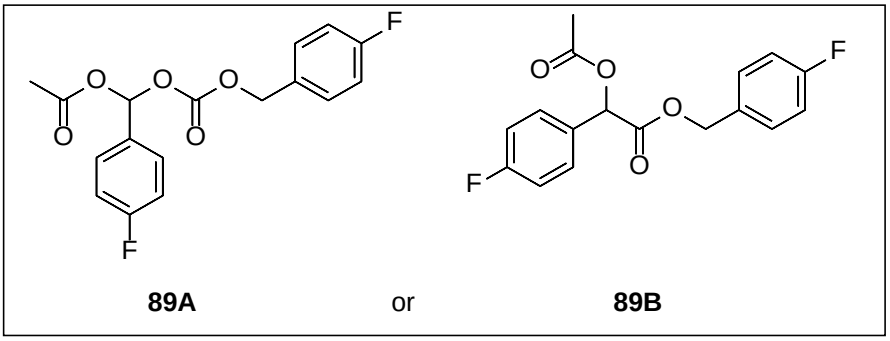


4-Fluorobenzaldehyde[22] **86**

Key signal observed: 1H s at δ_H 10 ppm.

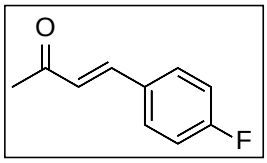
***Tentative assignment of first fraction* 89**

(See **Chapter 4 Results and Discussion**, **Section 4.1.3.7** for detailed ^{1}H NMR analysis)



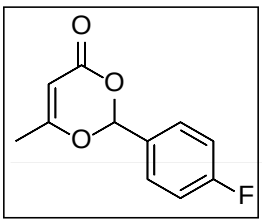
89A or **89B**

δ_H($CDCl_3$, 400 MHz): 2.17 (3H, s, CH_3), 5.17 (2H, apparent quartet, CH_2), 6.61 (1H, s, C*H*), 6.93-7.48 (8H, m, 8 x Ar-C*H*); δ_C($CDCl_3$, 100 MHz): 11.4 (*C*H_3), 65.6 (*C*H_2), 107.3 (*C*H), 128.5 (2 x Ar-*C*H), 128.6 (2 x Ar-*C*H), 130.4 (2 x Ar-*C*H), 130.5 (2 x Ar-*C*H), 134.5 (C_q), 134.6 (C_q), 134.9 (C_q), 137.0 (C_q), 149.5 (*C*=O), 160.3 (*C*=O); ν_{max}(ATR)/cm^{-1} 1741, 1698, 1488.



(*E*)-4-(4-fluorophenyl)but-3-en-2-one 87[23]

δ_H($CDCl_3$, 400 MHz): 2.38 [3H, s, C(O)CH_3], 6.65 (1H, d, *H*C=C*, J* 16.7), 7.04-7.13 (2H, m, Ar-*H*), 7.44-7.57 [3H, m, containing (1H, d, C=C*H*), (2H, m, Ar-*H*); δ_C($CDCl_3$, 100 MHz): 27.6 (*C*H_3), 116.1 (2 x Ar-*C*H, d, $^2J_{CF}$ 22 Hz), 126.8 (*C*H - alkene), 130.1 (2 x Ar-*C*H, d, $^3J_{CF}$ 8 Hz), 130.6 (C_q, d, $^4J_{CF}$ 3), 142.1 (*C*H - alkene), 164.0 (C_q, d, $^1J_{CF}$ 252), 198.2 (*C*=O) ketone; ν_{max}(ATR)/cm^{-1} 1692, 1666, 1597; HRMS (ES+): Exact mass calculated for $C_{10}H_{10}OF$ $[M+H]^+$ 165.0716. Found 165.0713; *m/z* (ES+) 165.3 [(M+H), 100%].



2-(4-fluorophenyl)-6-methyl-4H-1,3-dioxin-4-one 88

δ_H($CDCl_3$, 400 MHz): 2.12 (3H, s, CH_3), 5.44 (1H, s, C*H* alkene), 6.37 (1H, s, OC*H*), 7.11-7.19 (2H, m, Ar-*H*), 7.55-7.61 (2H, m, Ar-*H*); δ_C($CDCl_3$,100 MHz): 19.6 (*C*H_3), 96.6 (*C*H) alkene, 99.4 (O*C*H), 115.7 (2 x Ar-*C*H, d, $^2J_{CF}$ 22), 128.7 (2 x Ar-*C*H, d, $^3J_{CF}$ 8.7), 129.7 (C_q, d, $^4J_{CF}$ 3), 161.9 (C_q alkene), 163.8 (C_q, d, $^1J_{CF}$ 250), 171.9 (*C*=O); ν_{max}(ATR)/cm^{-1} 1719, 1627, 1432, 1378; HRMS (ES+): Exact mass calculated for $C_{11}H_{10}O_3F$ $[M+H]^+$ 209.0614. Found 209.0618; *m/z* (ES+) 209.3 [(M+H), 55%].

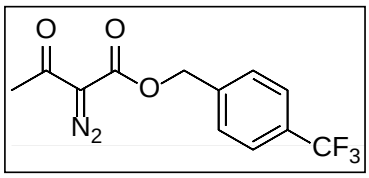
Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

Rhodium(II) acetate dimer (48 mg, 0.11 mmol, 5 mol %) was added to a stirring solution 4-fluorobenzyl 2-diazo-3-oxobutanoate **62** (0.51 g, 2.15 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), two identifiable fractions were obtained. (*E*)-4-(4-fluorophenyl)but-3-en-2-one **87** (42 mg, 12%), and the most polar fraction contained 2-(4-fluorophenyl)-6-methyl-4H-1,3-dioxin-4-one **88** (19 mg, 5%). Evidence for 4-fluorobenzaldehyde **86** was seen in the crude reaction mxture but it was not isolated after column chromatography. Spectral details as listed above.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

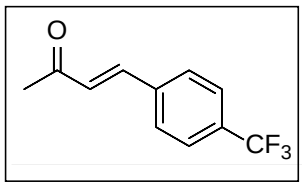
Rhodium(II) acetate dimer (22 mg, 0.06 mmol, 5 mol %) was added to a solution of 4-fluorobenzyl 2-diazo-3-oxobutanoate **62** (0.24 g, 1.02 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **63**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-70:30), two identifiable fractions were obtained. (*E*)-4-(4-fluorophenyl)but-3-en-2-one **87** (20 mg, 12%), and the most polar fraction contained 2-(4-fluorophenyl)-6-methyl-4H-1,3-dioxin-4-one **88** (10 mg, 5%). Evidence for 4-fluorobenzaldehyde **86** was seen in the crude reaction mxture but it was not isolated after column chromatography. Spectral details as listed above.

4.2.7 Decomposition of 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate 65



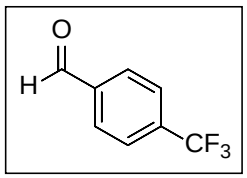
Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

Rhodium(II) acetate dimer (0.3 mg, 0.43 μmol, 0.04 mol %) was added to a stirring solution of 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65** (0.31 g, 1.08 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 5 Bar). Nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a brown oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-70:30), no identifiable products were isolated. Although evidence for 4-(4-(trifluoromethyl)phenyl)but-3-en-2-one **92** and 4-(trifluoromethyl)benzaldehyde **93** were observed in the ^{1}H NMR spectrum of the crude reaction mixture, they were not isolated.



4-(4-(Trifluoromethyl)phenyl)but-3-en-2-one[24] **92**

Key signal observed: 1H d at δ_H 6.69 ppm.



4-(Trifluoromethyl)benzaldehyde[25] **93**

Key signal observed: 1H s at δ_H 10.01 ppm.

Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

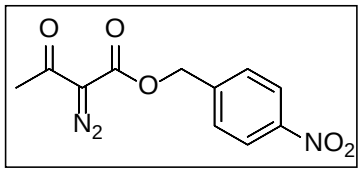
Rhodium(II) acetate dimer (37 mg, 0.08 mmol, 5 mol %) was added to a stirring solution of 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65** (0.48 g, 1.68 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), no identifiable products were isolated. Although evidence for 4-(4-(trifluoromethyl)phenyl)but-3-en-2-one **92** and 4-(trifluoromethyl)benzaldehyde **93** were observed in the ^{1}H NMR spectrum of the crude reaction mixture, they were not isolated.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

Rhodium(II) acetate dimer (40 mg, 0.09 mmol, 5 mol %) was added to a solution of 4-(trifluoromethyl)benzyl 2-diazo-3-oxobutanoate **65** (0.52 g, 1.09 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **92**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-70:30), no identifiable products were isolated. Although evidence for 4-

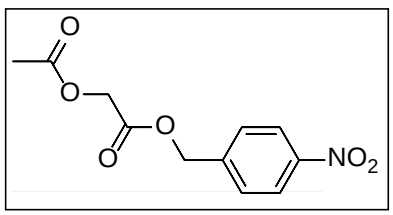
(trifluoromethyl)benzaldehyde **93** were observed in the ^{1}H NMR spectrum of the crude reaction mixture, it was not isolated.

4.2.8 Decomposition of 4-nitrobenzyl 2-diazo-3-oxobutanoate 64



Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

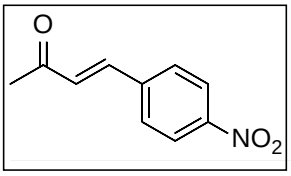
Rhodium(II) acetate dimer (0.4 mg, 0.43 µmol, 0.04 mol %) was added to a stirring solution of 4-nitrobenzyl 2-diazo-3-oxobutanoate **64** (0.31 g, 1.08 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 5 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a brown oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-70:30) gave one identifiable fractions. This contained 4-nitrobenzyl 2-acetoxyacetate **96** as a clear oil (27 mg, 10%). Although evidence for (*E*)-4-(4-nitrophenyl)but-3-en-2-one **94** and 4-nitrobenzaldehyde **95** were observed in the ^{1}H NMR spectrum of the crude reaction mixture, they were not isolated.



4-Nitrobenzyl 2-acetoxyacetate 96

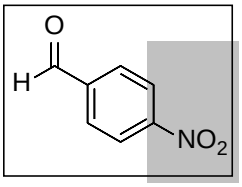
δ_H($CDCl_3$, 400 MHz): 2.62 (3H, s, CH_3), 5.32 (2H, s, CH_2), 5.82 (2H, s, CH_2), 7.56-7.58 (2H, d, Ar-C*H*), 8.24-8.25 (2H, d, Ar-C*H*); δ_C($CDCl_3$, 100 MHz): 14.7 (*C*H_3), 65.7 (*C*H_2), 74.3 (*C*H_2), 123.9 (Ar-*C*H), 128.1 (Ar-*C*H), 142.8 (C_q), 147.7 (C_q), 161.8 (*C*=O), 163.3 (*C*=O); ν_{max}(ATR)/cm$^-$

[1] 1737, 1702, 1602, 1518; HRMS (ES+): Exact mass calculated for $C_{11}H_{11}NO_6$ $[M+H]^+$ 254.0586. Found 254.0592; *m/z* (ES+) 254.4 [(M+H), 50%].



(*E*)-4-(4-Nitrophenyl)but-3-en-2-one[18] **94**

Key signal observed: 1H d at δ_H 6.7 ppm.



4-Nitrobenzaldehyde[26] **95**

Key signal observed: 1H s at δ_H 10 ppm.

Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

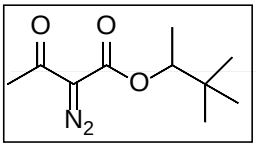
Rhodium(II) acetate dimer (41 mg, 0.0 mmol, 5 mol %) was added to a stirring solution of 4-nitrobenzyl 2-diazo-3-oxobutanoate **64** (0.48 g, 1.89 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), no identifiable products were isolated. Although evidence for (*E*)-4-(4-nitrophenyl)but-3-en-2-one **94** and 4-nitrobenzaldehyde **95** were observed in the ^{1}H NMR spectrum of the crude reaction mixture, they were not isolated.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

Rhodium(II) acetate dimer (47 mg, 0.11 mmol, 5 mol %) was added to a solution of 4-nitrobenzyl 2-diazo-3-oxobutanoate **64** (0.54 g, 2.13 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material. The dichloromethane solvent was

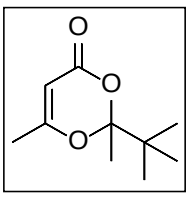
removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (95:5-70:30), no identifiable products were isolated. Although evidence for (*E*)-4-(4-nitrophenyl)but-3-en-2-one **94** and 4-nitrobenzaldehyde **95** were observed in the ^{1}H NMR spectrum of the crude reaction mixture, they were not isolated.

4.2.9 Decomposition of 3,3-dimethylbutan-2-yl 3-oxobutanoate 57



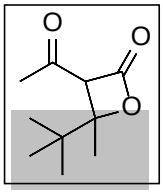
Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

Rhodium(II) acetate dimer (0.4 mg, 0.94 µmol, 0.04 mol %) was added to a stirring solution of 3,3-dimethylbutan-2-yl 3-oxobutanoate **57** (0.49 g, 2.35 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 7 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30) gave one identifiable fraction. The fraction contained 2-(*t*-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **97** (52 mg, 12%) as a clear oil. 3-Acetyl-4-(tert-butyl)-4-methyloxetan-2-one **100** was observed by ^{1}H NMR in the crude reaction mixture but was not isolated following column chromatography.



2-(*t*-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one[27] **97**

δ_H($CDCl_3$, 400 MHz): 1.09 (9H, s, 3 x CH_3), 1.59 (3H, s, CH_3), 1.98 (3H, s, CH_3), 5.19 (1H, s, C*H* alkene); δ_C($CDCl_3$, 100 MHz): 16.5 (*C*H_3), 19.9 (*C*H_3), 24.4 (3 x *C*H_3), 38.9 (C_q), 93.3 (*C*H) alkene, 111.6 (C_q), 161.4 (C_q) alkene, 168.7 (*C*=O); ν_{max}(ATR)/cm^{-1} 1737, 1447, 1372; HRMS (ES+): Exact mass calculated for $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178. Found 185.1169; *m/z* (ES+) 185.4 [(M+H), 50%], 207.3 [(M+Na), 40%], (ES-) 183.4 [(M-H), 20%].



3-Acetyl-4-(tert-butyl)-4-methyloxetan-2-one 100

Key signal observed: 1H s at δ_H 4.22 ppm.

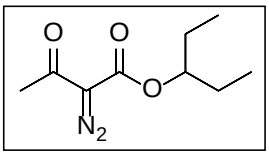
Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

Rhodium(II) acetate dimer (27 mg, 0.06 mmol, 5 mol %) was added to a stirring solution of 3,3-dimethylbutan-2-yl 3-oxobutanoate **57** (0.26 g, 1.21 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), no identifiable products were isolated. 3-Acetyl-4-(tert-butyl)-4-methyloxetan-2-one **100** was observed by ^{1}H NMR in the crude reaction mixture but was not isolated following column chromatography.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

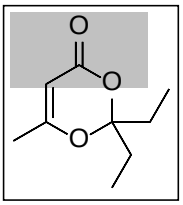
Rhodium(II) acetate dimer (25 mg, 0.06 mmol, 5 mol %) was added to a solution 3,3-dimethylbutan-2-yl 3-oxobutanoate **57** (0.24 g, 1.12 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **57**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (80:20-70:30), no identifiable products were isolated.

4.2.10 Decomposition of pentan-3-yl 2-diazo-3-oxobutanoate 67



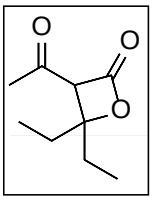
Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

Rhodium(II) acetate dimer (0.4 mg, 0.94 µmol, 0.04 mol %) was added to a stirring solution of pentan-3-yl 2-diazo-3-oxobutanoate **67** (0.48 g, 2.39 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 8 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), no identifiable products were isolated. Although evidence for 2,2-diethyl-6-methyl-4H-1,3-dioxin-4-one **101** and 3-acetyl-4,4-diethyloxetan-2-one **102** were observed in the ^{1}H NMR spectrum of the crude reaction mixture, they were not isolated.



2,2-Diethyl-6-methyl-4H-1,3-dioxin-4-one[28] **101**

Key signal observed: 1H s at δ_H 5.19 ppm.



3-Acetyl-4,4-diethyloxetan-2-one 102

Key signal observed: 1H s at δ_H 4.21 ppm.

Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

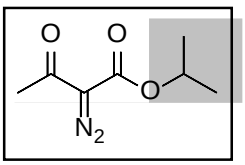
Rhodium(II) acetate dimer (27 mg, 0.06 mmol, 5 mol %) was added to a stirring solution of pentan-3-yl 2-diazo-3-oxobutanoate **67** (0.26 g, 1.21 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the

crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), no identifiable products were isolated. Although evidence for 3-acetyl-4,4-diethyloxetan-2-one **102** was observed in the ^{1}H NMR spectrum of the crude reaction mixture, it was not isolated.

Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

Rhodium(II) acetate dimer (25 mg, 0.06 mmol, 5 mol %) was added to a solution pentan-3-yl 2-diazo-3-oxobutanoate **67** (0.24 g, 1.12 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **57**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (80:20-70:30), no identifiable products were isolated.

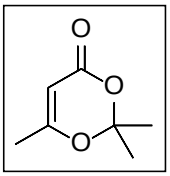
4.2.11 Decomposition of isopropyl 2-diazo-3-oxobutanoate 44



Method 1: Using 0.04 mol % $Rh_2(OAc)_4$ under MW irradiation

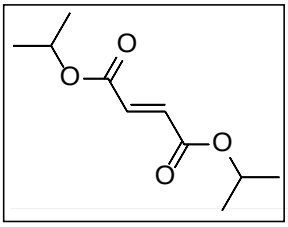
Rhodium(II) acetate dimer (0.5 mg, 0.94 µmol, 0.04 mol %) was added to a stirring solution of isopropyl 2-diazo-3-oxobutanoate **44** (0.53 g, 3.13 mmol) in dichloromethane (3 mL) at room temperature. The reaction mixture was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~ 7 Bar). Vigorous nitrogen gas evolution was observed upon releasing the pressure in the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude products shows a complex mixture of products. Purification by chromatography on silica gel using hexane-ethyl acetate (80:20) gave two

identifiable fraction. The less polar compound fraction contained 2-(*t*-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **49** (44 mg, 10%) as a clear oil, and the second fraction contained diisopropyl maleate **103** (72 mg, 11 %) as a pale yellow oil.



2,2,6-trimethyl-4H-1,3-dioxin-4-one[29] **49**

δ_H($CDCl_3$, 300 MHz): 1.69 (6H, s, 2 x C*H*$_3$), 1.99 (3H, s, C*H*$_3$), 5.24 (1H, s, C*H* alkene); δ_C($CDCl_3$, 75.5 MHz): 19.8 (*C*H$_3$), 24.9 (2 x *C*H$_3$), 93.7 (*C*H) alkene, 106.3 (C_q), 161.1 (C_q) alkene, 168.7 (*C*=O); ν_{max}(ATR)/cm^{-1} 1737, 1372; HRMS (ES+): Exact mass calculated for $C_7H_{11}O_3$ $[M+H]^+$ 143.0708. Found 143.0651; *m/z* (ES+) 165.3 [(M+H), 50%], (ES-) 141.3 [(M-H), 10%].



Diisopropyl maleate[30] **103**

δ_H($CDCl_3$, 300 MHz): 1.29 (12H, d, 4 x C*H*$_3$, *J* 6.3), 5.12 (2H, sept, 2 x C*H*, *J* 6.3), 6.18 (H, s, 2 x C*H* alkene); δ_C($CDCl_3$, 75.5 MHz): 21.7 (4 x *C*H$_3$), 68.9 (2 x *C*H), 130.3 (2 x *C*H) alkene, 164.8 (*C*=O); ν_{max}(ATR)/cm^{-1} 2999, 1721, 947; HRMS (ES+): Exact mass calculated for $C_{10}H_{17}O_4$ $[M+H]^+$ 201.1049. Found 201.1023; *m/z* (ES+) 201.3 [(M+H), 60%], (ES-) 199.3 [(M-H), 15%].

Method 2: Under reflux heating using 5 mol % $Rh_2(OAc)_4$

Rhodium(II) acetate dimer (67 mg, 0.15 mmol, 5 mol %) was added to a stirring solution of isopropyl 2-diazo-3-oxobutanoate **44** (0.52 g, 3.06 mmol) in dichloromethane (10 mL) at room temperature. The reaction was heated under reflux (45 °C) under an inert nitrogen atmosphere. TLC analysis after 90 min indicated complete consumption of the diazocarbonyl starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using gradient hexane-ethyl acetate (90:10-70:30), one fraction was isolated which contained 2-(*t*-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **49** with a mixture of other decomposition products.

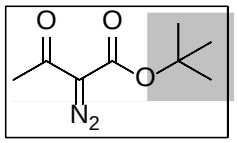
Method 3: Using 5 mol % $Rh_2(OAc)_4$ at r.t. for 18 h

Rhodium(II) acetate dimer (31 mg, 0.07 mmol, 5 mol %) was added to a solution isopropyl 2-diazo-3-oxobutanoate **44** (0.24 g, 1.41 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred under an inert nitrogen atmosphere for 18 h after which time TLC analysis of the crude reaction material showed complete consumption of the diazocarbonyl starting material **44**. The dichloromethane solvent was removed under reduced pressure to give the crude reaction products as a dark green oil. The ^{1}H NMR spectrum of the crude reaction mixture shows a complex mixture of products. Following purification by chromatography on silica gel using hexane-ethyl acetate (80:20), one fraction was isolated which contained 2-(*t*-butyl)-2,6-dimethyl-4H-1,3-dioxin-4-one **49** with a mixture of other decomposition products.

4.3 Attempted OH insertions

4.3.1 Gadolinium (III) acetate catalysed reactions

4.3.1.1 Gadolinium (III) acetate at room temperature



Method 1: Using 1 mol% $Gd(OAc)_3$ at r.t.

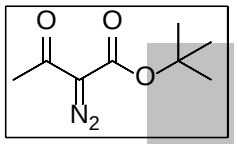
Gadolinium (III) acetate (3.3 mg, 0.01 mmol, 1 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 10 mmol) in dichloromethane (3 mL) under an inert nitrogen atmosphere. The reaction was stirred at room temperature for 48 h, while being monitored by TLC analysis. After 48h, TLC analysis indicated no consumption of starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a pale yellow oil. NMR analysis confirmed that the reaction mixture contained starting material only.

Entry[a]	Catalyst	Catalyst Loading (mol %)	Time	Result
1	$Gd(OAc)_3$	1	48	No reaction
2	$Gd(OAc)_3$	5	48	No reaction

3	$Gd(OAc)_3$	10	48	No reaction

[a] Reactions typically carried out on a 1 mmol scale in dichloromethane

4.3.1.2 Gadolinium (III) acetate at reflux (45 °C)

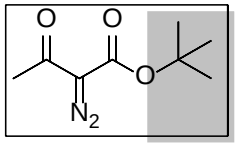


Method 2: Using 1 mol% $Gd(OAc)_3$ at reflux (45 °C)

Gadolinium (III) acetate (3.3 mg, 0.01 mmol, 1 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 10 mmol) in dichloromethane (3 mL). The reaction mixture was refluxed at 45 °C for 19.5h, at which time TLC analysis indicated no consumption of starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a pale yellow oil. NMR analysis confirmed that the reaction mixture contained starting material only.

Entry[a]	Catalyst	Catalyst Loading (mol %)	Temperature °C	Time	Result
1	$Gd(OAc)_3$	1	45	19.5	No reaction
2	$Gd(OAc)_3$	5	45	24	No reaction
3	$Gd(OAc)_3$	10	45	24	No reaction

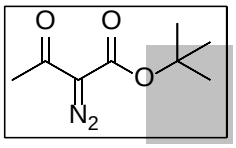
4.3.1.3 Gadolinium (III) acetate under MW irradiation



Using 1 mol% $Gd(OAc)_3$ under MW irradiation

Gadolinium (III) acetate (3.3 mg, 0.01 mmol, 1 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.09 g, 1 mmol) in dichloromethane (3 mL). The reaction was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~6 Bar). Some nitrogen gas evolution was observed as the pressure was released from the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a brown oil. Following column chromatography on silica gel using 80:20

hexane: ethyl acetate two identifiable fractions were isolated. The least polar fraction contained a mixture of unidentifiable decomposition products. The next fraction contained unreacted *t*-butyl 2-diazo-3-oxobutanoate **12** (0.15 g, 83%). The final fraction contained phenol as an off-white solid (0.06 g, 69%).

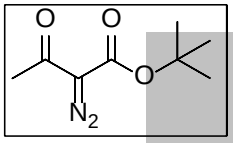


Using 5 mol% $Gd(OAc)_3$ under MW irradiation

Gadolinium (III) acetate (16.5 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.09 g, 1 mmol) in dichloromethane (3 mL). The reaction was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~6 Bar). Some nitrogen gas evolution was observed as the pressure was released from the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a brown oil. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate two identifiable fractions were isolated. The least polar fraction contained unidentifiable decomposition products. The next fraction contained unreacted *t*-butyl 2-diazo-3-oxobutanoate **12** (0.14 g, 80%). The final fraction contained phenol **117** as an off-white solid (0.07 g, 80%). Additional fractions contained unidentifiable decomposition products.

4.3.2 Erbium (III) triflate catalysed reactions

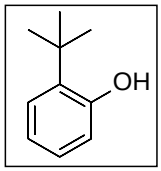
4.3.2.1 Erbium (III) triflate at room temperature



Using 1 mol% $Er(OTf)_3$ at r.t.

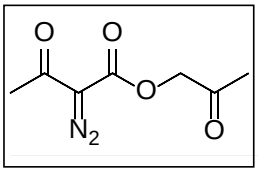
Erbium(III) triflate (6.1 mg, 0.01 mmol, 1 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 10 mmol) in dichloromethane (3 mL) under an inert nitrogen atmosphere. The reaction was stirred at room temperature for 48 h, while being monitored by TLC analysis. After 48h, TLC analysis indicated only partial consumption of starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a pale yellow oil. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate three identifiable fractions were isolated. The least polar fraction contained 2-(*t*-

butyl)phenol **118** (4 mg, 8%). The next fraction contained unreacted phenol **117** (0.61 g, 65%) as an off-white solid. The most polar fraction contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (54.3 mg, 30%) as a dark yellow solid.



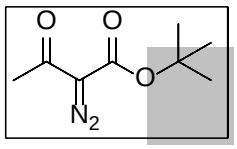
2-(*t*-Butyl)phenol[31] **118**

δ_H($CDCl_3$, 400 MHz): 1.41 (9H, s, 3 x C*H*$_3$), 4.78 (1H, br s, O*H*), 6.64-6.68 (1H, dd, Ar-C*H*, *J* 7.9, 1.3), 6.87-6.90 (1H, td, Ar-C*H*, *J* 7.6, 1.), 7.04-7.10 (1H, td, Ar-C*H*, *J* 7.5, 1.6), 7.24-7.29 (1H, dd, Ar-C*H*, *J* 7.9, 1.6); δ_C($CDCl_3$, 100 MHz): 29.6 (3 x *C*H$_3$), 34.5 (*C*$_q$), 116.5 (Ar-*C*H), 120.6 (Ar-*C*H), 127.0 (Ar-*C*H), 127.1 (Ar-*C*H), 136.1 (Ar-*C*q), 154.2 (Ar-C-OH); HRMS (ES+): Exact mass calculated for $C_{10}H_{15}O$ $[M+H]^+$ 151.1123. Found 151.1118; *m/z* (ES-) 149.3 [(M -H), 100 %].



2-Oxopropyl 2-diazo-3-oxobutanoate[32] **119**

δ_H($CDCl_3$, 400 MHz): 2.20 (3H, s, C*H*$_3$), 2.48 (3H, s, C*H*$_3$), 4.82 (2H, s, C*H*$_2$); δ_C($CDCl_3$, 100 MHz): 25.9 (*C*H$_3$), 28.2 (*C*H$_3$), 68.4 (*C*H$_2$), 160.7 (*C*=O) ester, 189.6 (*C*=O) ketone, 200.3 (*C*=O) ketone, no signal observed for (*C*=N$_2$); ν_{max}(ATR)/cm^{-1} 2136, 1729, 1713, 1680; HRMS (ES+): Exact mass calculated for $C_7H_9O_4N_2$ $[M+H]^+$ 185.0562. Found 185.0557; *m/z* (ES+) 185.3 [(M +H), 20 %], 207.2 [(M +Na), 100%].

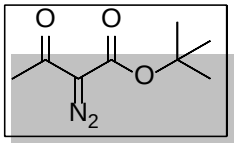


Using 5 mol% Er(OTf)$_3$ at r.t.

Erbium(III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 10 mmol) in dichloromethane (3 mL) under an inert nitrogen atmosphere. The reaction was stirred at room temperature for 48 h, while being monitored by TLC analysis. After 48h, TLC analysis indicated only partial consumption of starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a pale yellow oil. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate three identifiable fractions were isolated. The least polar fraction contained 2-(*t*-butyl)phenol **118** (30.6 mg, 20%). The next fraction contained unreacted phenol **117** (0.53 g, 56%) as an off-white solid. The most polar fraction contained 2-oxopropyl 2-diazo-3-

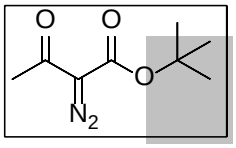
oxobutanoate **119** (56 mg, 30%) as a dark yellow solid. Spectral characteristics were consistent with those previously reported.

4.3.2.2 Erbium (III) triflate at reflux



Using 1 mol% $Er(OTf)_3$ at reflux (45 °C)

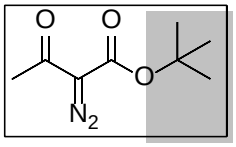
Erbium(III) triflate (6.1 mg, 0.01 mmol, 1 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 10 mmol) in dichloromethane (3 mL). The reaction mixture was refluxed at 45 °C for 24h. The solution was cooled and the dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark brown oil. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate three identifiable fractions were isolated. The least polar fraction contained 2-(*t*-butyl)phenol **118** (22.9 mg, 15%). The next fraction contained unreacted phenol **117** (0.59 g, 63%) as an off-white solid. The most polar fraction contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (34 mg, 18%) as a dark yellow solid. Spectral characteristics were consistent with those previously reported.



Using 5 mol% $Er(OTf)_3$ at reflux (45 °C)

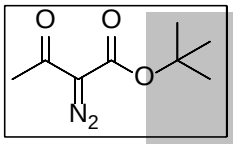
Erbium(III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 10 mmol) in dichloromethane (3 mL). The reaction mixture was refluxed at 45 °C for 24h. The solution was cooled and the dichloromethane was removed under reduced pressure to give the crude reaction mixture as a dark brown oil. Following column chromatography on silica gel using 70:30 hexane: ethyl acetate three identifiable fractions were isolated. The least polar fraction contained 2-(*t*-butyl)phenol **118** (20 mg, 13%). The next fraction contained unreacted phenol **117** (0.55 g, 59%) as an off-white solid. The most polar fraction contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (50.0 mg, 27%) as a dark yellow oil. Spectral characteristics were consistent with those previously reported.

4.3.2.3 Erbium (III) triflate under MW irradiation



Using 1 mol% $Er(OTf)_3$ under MW irradiation

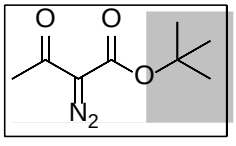
Erbium(III) triflate (6.1 mg, 0.01 mmol, 1 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 1 mmol) in dichloromethane (3 mL). The reaction was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~6 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a dark brown oil. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate two identifiable fractions were isolated. The first fraction contained *t*-butyl 2-diazo-3-oxobutanoate **12** (0.10 g, 54%). The more polar fraction contained unreacted phenol **117** (0.05 g, 53%) as an off-white solid. Other fractions contained unidentifiable decomposition products. Spectral characteristics were consistent with those previously reported.



Using 5 mol% $Er(OTf)_3$ under MW irradiation

Erbium(III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.94g, 1 mmol) in dichloromethane (3 mL). The reaction was heated to 100 °C under microwave irradiation for 3 min in a sealed microwave tube (pressure ~7 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a dark brown oil. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate three identifiable fractions were isolated. The first fraction contained *t*-butyl 2-diazo-3-oxobutanoate **12** (0.11 g, 60%). The next fraction contained unreacted phenol 117 (0.55 g, 59%) as an off-white solid. The most polar fraction contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (36 mg, 24%) as a dark yellow oil. Spectral characteristics were consistent with those previously reported.

4.4 Attempted SH insertions



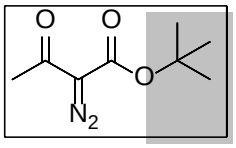
Method 1: Using 1 mol% $Gd(OAc)_3$ at r.t.

Gadolinium (III) acetate (3.3 mg, 0.01 mmol, 1 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and thiophenol **120** (0.11g, 1 mmol) in dichloromethane (3 mL) under an inert nitrogen atmosphere. The reaction was stirred at room temperature for 78 h, while being monitored

by TLC analysis. After 78h, TLC analysis indicated no consumption of starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.

Entry[a]	Catalyst	Catalyst Loading (mol %)	Time	Product
1	$Gd(OAc)_3$	1	78	No reaction
2	$Gd(OAc)_3$	5	78	No reaction

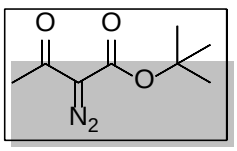
[a] Reactions typically carried out on a 1 mmol scale in dichloromethane



Method 2: Using 1 mol% $Gd(OAc)_3$ at reflux (45 °C)

Gadolinium (III) acetate (3.3 mg, 0.01 mmol, 1 mol %) was added to a stirring solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and thiophenol (0.11g, 1 mmol) in dichloromethane (3 mL) under an inert nitrogen atmosphere. The reaction mixture was refluxed at 45 °C for 24h, at which time TLC analysis indicated no consumption of starting material. The dichloromethane was removed under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.

Entry[a]	Catalyst	Catalyst Loading (mol %)	Temperature °C	Time	Product
1	$Gd(OAc)_3$	1	45	24	No reaction
2	$Gd(OAc)_3$	5	45	24	No reaction

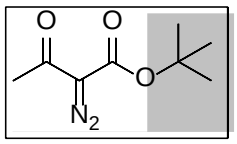


Using 1 mol% $Gd(OAc)_3$ under MW irradiation

Gadolinium (III) acetate (3.3 mg, 0.01 mmol, 1 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and

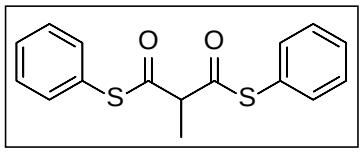
thiophenol **120** (0.11g, 1 mmol) in dichloromethane (3 mL). The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~6 Bar). Some nitrogen gas evolution was observed as the pressure was released from the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.

Entry[a]	Catalyst	Catalyst Loading (mol %)	Temperature °C	Time	Result
1	$Gd(OAc)_3$	1	100	10	No reaction
2	$Gd(OAc)_3$	5	100	10	No reaction



Using 1 mol% $Gd(OAc)_3$ under MW irradiation

Gadolinium (III) acetate (3.3 mg, 0.01 mmol, 1 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and thiophenol **120** (0.11g, 1 mmol) in dichloromethane (3 mL). The reaction was heated to 100 °C under microwave irradiation for 40 min in a sealed microwave tube (pressure ~8 Bar). Some nitrogen gas evolution was observed as the pressure was released from the microwave vial. The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate one identifiable fraction was isolated. This contained *S,S*-diphenyl 2-methylpropanebis(thioate) **121** (0.03 g, 10%) as a dark yellow oil.

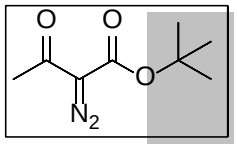


***S,S*-Diphenyl 2-methylpropanebis(thioate)**[33] **121**

δ_H($CDCl_3$, 400 MHz): 1.59 (3H, d, C*H*$_3$, *J* 6.9), 4.07 (1H, q, C*H*, *J* 6.9), 7.40-7.48 (10H, m, 10 x Ar-*H*); δ_C($CDCl_3$, 100 MHz): 14.8 (*C*H$_3$), 61.5 (*C*H), 126.8 (2 x *C*q), 129.4 (2 x Ar-*C*H), 129.8 (4 x Ar-*C*H), 134.5 (4 x Ar-*C*H), 192.9 (2 x *C*=O) thioester, HRMS (ES+): Exact mass calculated for $C_{16}H_{15}O_2S_2$ $[M+H]^+$ 303.0513. Found 303.0502; *m/z* (ES+) 325.1 [(M +Na), 100 %].

4.5 Studies on reactivity using various catalysts under microwave irradiation

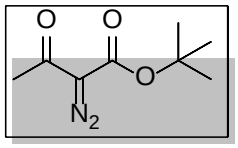
4.5.1 Catalyst Free



Microwave Irradiation in the absence of a catalyst

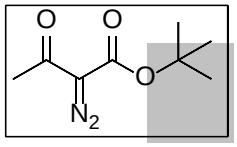
A solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.09 g, 1 mmol) in dichloromethane (3 mL) was placed in a sealed microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~8 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis showed no reaction had occurred, with only starting material present in the mixture.

4.5.2 Gadolinium (III) acetate



Using 5 mol% Gd(OAc)$_3$ under microwave irradiation

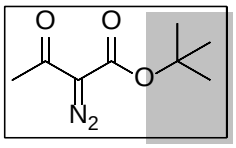
Gadolinium (III) acetate (16.7 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~6 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis showed no reaction had occurred, with only starting material present in the mixture.



Using 5 mol% Gd(OAc)$_3$ under microwave irradiation with phenol

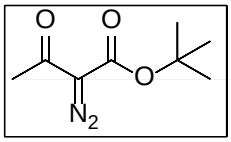
Gadolinium (III) acetate (16.7 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.09 g, 1 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~5 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis showed no reaction had occurred, with only starting material present in the mixture.

4.5.3 Gadolinium (III) triflate



Using 5 mol% $Gd(OTf)_3$ under microwave irradiation

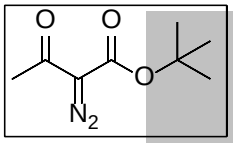
Gadolinium (III) triflate (3.3 mg, 0.01 mmol, 1 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~7 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture showed some decomposition had occurred. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate one identifiable fraction was isolated. This contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (48.5 mg, 26%) as a dark yellow solid. Additional fractions contained unidentifiable decomposition products. Spectral characteristics were consistent with those previously reported.



Using 5 mol% $Gd(OTf)_3$ under microwave irradiation with phenol

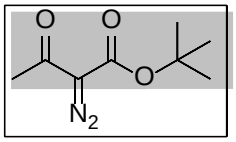
Gadolinium (III) triflate (30.2 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.09 g, 1 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~9 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a brown oil. ^{1}H NMR analysis showed formation of an unknown product. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate two identifiable fractions were isolated. The less polar fraction contained unreacted phenol **117** (0.08, 85%) as an off-white solid. The more polar fraction contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (54.3 mg, 30%) as a dark yellow solid. An additional fraction contained unidentifiable decomposition products. Spectral characteristics were consistent with those previously reported.

4.5.4 Erbium (III) triflate



Using 5 mol% Er(OTf)$_3$ under microwave irradiation

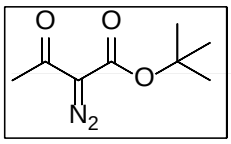
Erbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~7 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture showed some decomposition had occurred. Following column chromatography on silica gel using 50:50 hexane: ethyl acetate one identifiable fraction was isolated. This contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (50.1 mg, 27%) as a dark yellow solid. Additional fractions contained unidentifiable decomposition products. Spectral characteristics were consistent with those previously reported.



Using 5 mol% Er(OTf)$_3$ under microwave irradiation with phenol

Erbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.09 g, 1 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~7 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a brown oil. ^{1}H NMR analysis showed formation of an unknown product. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate two identifiable fractions were isolated. The less polar fraction contained unreacted phenol **117** (0.07 g, 74%) as an off-white solid. The more polar fraction contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (54.3 mg, 30%) as a dark yellow solid. Spectral characteristics were consistent with those previously reported.

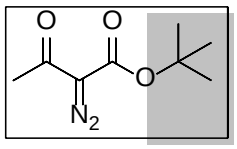
4.5.5 Ytterbium (III) triflate



Using 5 mol% Yb(OTf)$_3$ under microwave irradiation

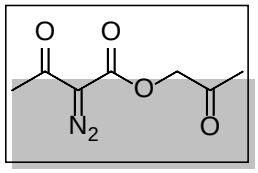
Ytterbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under

microwave irradiation for 10 min in a sealed microwave tube (pressure ~7 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture showed some decomposition had occurred. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate one identifiable fraction was isolated. This contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (58.2 mg, 32%) as a dark yellow solid. An additional fraction contained unidentifiable decomposition products. Spectral characteristics were consistent with those previously reported.



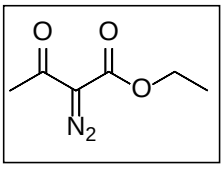
Using 5 mol% Yb(OTf)$_3$ under microwave irradiation with phenol

Ytterbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of *t*-butyl 2-diazo-3-oxobutanoate **12** (0.18 g, 1.00 mmol) and phenol **117** (0.09 g, 1 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 10 min in a sealed microwave tube (pressure ~7 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a brown oil. ^{1}H NMR analysis showed formation of an unknown product. Following column chromatography on silica gel using 80:20 hexane: ethyl acetate two fractions were isolated. The less polar fraction contained unreacted phenol **117** (0.07 g, 77%) as an off-white solid. The more polar fraction contained 2-oxopropyl 2-diazo-3-oxobutanoate **119** (54.6 mg, 30%) as a dark yellow solid. Spectral characteristics were consistent with those previously reported.



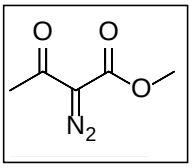
Using 5 mol% Er(OTf)$_3$ under microwave irradiation

Erbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of 2-oxopropyl 2-diazo-3-oxobutanoate **119** (0.18 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 20 min in a sealed microwave tube (pressure ~2 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.



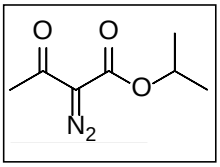
Using 5 mol% $Er(OTf)_3$ under microwave irradiation

Erbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of 2-oxopropyl 2-diazo-3-oxobutanoate **119** (0.16 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 20 min in a sealed microwave tube (pressure ~1 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.



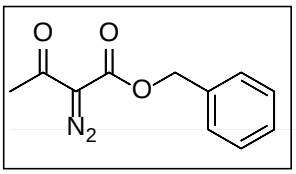
Using 5 mol% $Er(OTf)_3$ under microwave irradiation

Erbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of methyl 2-diazo-3-oxobutanoate **125** (0.14 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 20 min in a sealed microwave tube (pressure ~2 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.



Using 5 mol% $Er(OTf)_3$ under microwave irradiation

Erbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of isopropyl 2-diazo-3-oxobutanoate **44** (0.17 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 20 min in a sealed microwave tube (pressure ~2 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.



Using 5 mol% $Er(OTf)_3$ under microwave irradiation

Erbium (III) triflate (30.7 mg, 0.05 mmol, 5 mol %) was added to a solution of benzyl 2-diazo-3-oxobutanoate **46** (0.22 g, 1.00 mmol) in dichloromethane (3 mL) in a microwave tube. The reaction was heated to 100 °C under microwave irradiation for 20 min in a sealed microwave tube (pressure

~2 Bar). The reaction mixture was cooled and concentrated under reduced pressure to give the crude reaction mixture as a pale yellow oil. ^{1}H NMR analysis confirmed that the reaction mixture contained starting material only.

4.6 References

[1] R. H. Tale, R. N. Adude, *Tetrahedron Lett.* **2006**, *47*, 7263–7265.

[2] J. Holz, A. Monsees, H. Jiao, J. You, I. V Komarov, C. Fischer, K. Drauz, A. Boerner, *J. Org. Chem.* **2003**, *68*, 1701–1707.

[3] V. V Feofilaktov, *Izv. Akad. Nauk SSSR, Seriya Khimicheskaya* **1941**, 521–530.

[4] P. Lacotte, C. Puente, Y. Ambroise, *ChemMedChem* **2013**, *8*, 104–111.

[5] G. B. Dharma Rao, B. N. Acharya, M. P. Kaushik, *Tetrahedron Lett.* **2013**, *54*, 6644–6647.

[6] Y. Ueda, G. Roberge, V. Vinet, *Can. J. Chem.* **1984**, *62*, 2936–2940.

[7] G. C. M. Kondaiah, L. A. Reddy, K. S. Babu, V. M. Gurav, K. G. Huge, R. Bandichhor, P. P. Reddy, A. Bhattacharya, R. V. Anand, *Tetrahedron Lett.* **2008**, *49*, 106–109.

[8] J. Soleil, V. Loppinet, *Chim. Ther.* **1966**, 309–313.

[9] M. Risso, M. Mazzini, S. Kroger, P. Saenz-Mendez, G. Seoane, D. Gamenara, *Green Chem. Lett. Rev.* **2012**, *5*, 539–543.

[10] Z.-H. Qu, W.-F. Shi, X.-L. Jin, J.-B. Wang, *Youji Huaxue* **2003**, *23*, 988–995.

[11] X. Xu, X. Wang, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* **2015**, *17*, 790–793.

[12] M. E. Meyer, E. M. Ferreira, B. M. Stoltz, *Chem. Commun.* **2006**, 1316–1318.

[13] K. Sato, A. Tarui, S. Matsuda, M. Omote, A. Ando, I. Kumadaki, *Tetrahedron Lett.* **2005**, *46*, 7679–7681.

[14] S. B. Solabannavar, U. V Desai, R. B. Mane, *Indian J. Chem. Sect. B Org. Chem. Incl. Med. Chem.* **2004**, *43B*, 2235–2237.

[15] E. V Dehmlow, A. R. Shamout, *Liebigs Ann. der Chemie* **1982**, 1753–1755.

[16] B. Jiang, S.-J. Tu, P. Kaur, W. Wever, G. Li, *J. Am. Chem. Soc.* **2009**, *131*, 11660–11661.

[17] R. Cano, M. Yus, D. J. Ramon, *Tetrahedron* **2011**, *67*, 8079–8085.

[18] M. Iinuma, K. Moriyama, H. Togo, *Tetrahedron* **2013**, *69*, 2961–2970.

[19] M. Viviano, T. N. Glasnov, B. Reichart, G. Tekautz, C. O. Kappe, *Org. Process Res. Dev.* **2011**, *15*, 858–870.

[20] W. Yin, C. Chu, Q. Lu, J. Tao, X. Liang, R. Liu, *Adv. Synth. Catal.* **2010**, *352*, 113–118.

[21] S. Dhuru, D. Bhedi, D. Gophane, K. Hirbhagat, V. Nadar, D. More, S. Parikh, R. Dalal, L. C. Fonseca, F. Kharas, et al., *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3784–3787.

[22] T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chemie, Int. Ed.* **2008**, *47*, 5993–5996, S5993/1–S5993/78.

[23] M. McConville, O. Saidi, J. Blacker, J. Xiao, *J. Org. Chem.* **2009**, *74*, 2692–2698.

[24] S. Piri, M. R. Poorheravi, *Asian J. Chem.* **2010**, *22*, 8002–8006.

[25] P. V. Ramachandran, A. Chatterjee, *Org. Lett.* **2008**, *10*, 1195–1198.

[26] Y. Kubota, H. Yamaguchi, T. Yamada, S. Inagaki, Y. Sugi, T. Tatsumi, *Top. Catal.* **2010**, *53*, 492–499.

[27] N. Haddad, I. Rukhman, Z. Abramovich, *J. Org. Chem.* **1997**, *62*, 7629–7636.

[28] A. E. May, T. R. Hoye, *J. Org. Chem.* **2010**, *75*, 6054–6056.

[29] M. Rodrigues, R. Pinol, G. Antorrena, C. D. S. Brites, N. J. O. Silva, J. L. Murillo, R. Cases, I. Diez, F. Palacio, N. Torras, et al., *Adv. Funct. Mater.* **2016**, *26*, 200–209.

[30] H. Valizadeh, E. Khalili, *J. Iran. Chem. Soc.* **2012**, *9*, 529–534.

[31] X. Li, R. Cao, Q. Lin, *Green Chem. Lett. Rev.* **2014**, *7*, 179–183, 6 pp.

[32] A. Padwa, D. C. Dean, D. J. Fairfax, S. L. Xu, *J. Org. Chem.* **1993**, *58*, 4646–4655.

[33] K. Matsuo, M. Shindo, *Org. Lett.* **2011**, *13*, 4406–4409.